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Description

The present invention relates to novel compounds and anticancer drug potentiaters containing them as effective components.

Since the number of cancer patients is increasing year after year and cancer is the leading death cause today in many countries, cancer treatment is of great social interest.

Research and development regarding anticancer drugs for cancer treatment have been actively pursued and various anticancer drugs have been clinically used for therapeutic benefit. The effect of these agents steadily improves from year to year. However, in many cases, the agents do not necessarily completely control cancer growth and prolong the life of cancer patients. Furthermore, the use of multiple anticancer drugs in combination (multiple-drug treatment) have been tried in various clinical cases. However, likewise, the resulting effect is not entirely satisfactory cancer chemotherapy. Thus, development of novel therapeutic agents for the treatment of cancer from a fresh viewpoint is needed.

Development of more effective anticancer drugs or of means to deliver anticancer drugs more selectively to the target organs and tissues continues. Today, various research activities directed towards these goals are being conducted in many places throughout the world but only with increasing difficulty.

Another important aspect of cancer chemotherapy is potentiating the effects of chemotherapeutic agents. Development of potentiaters to facilitate presently available anticancer drugs, in particular for multiple drug-resistant cancers which is a serious clinical problem in cancer chemotherapy, is considered to be extremely important in cancer therapy. The background of the clinical incidence of resistance of cancer to anticancer drugs is complex. Clinically, two aspects are generally considered. The first is where the resistance is attributed to individual cancer patients. The second is where the resistance is attributed to cancer cells per se. Recently, as to the second aspect, the mechanism of tumor cell resistance has been elucidated at a molecular level and accordingly methods for therapy of this type of cancer resistance have been under investigation. Namely, a gene which is responsible for multi-drug-resistance has been recently isolated. It has been determined that this gene codes for a membrane protein, P-glycoprotein, and is expressed in multi-drug-resistant cells. It is suspected that the P-glycoprotein functions by promoting extracellular excretion of anticancer drugs and plays the central role in the mechanism of multiple-drug-resistance. Furthermore, it is suggested that the mechanism is partly common to that of the resistance to solid cancer which is by itself resistant to anticancer drugs.

Anticancer drugs primarily pass into the cell membrane to manifest their effect inside the cells; however, in drug-resistant cancer cells, anticancer drugs are discharged outside the cells due to the function of the P-glycoprotein, so that the drug concentration inside the cancer cells remains low. Consequently, the effect of the anticancer drugs is not exhibited to the fullest extent possible.

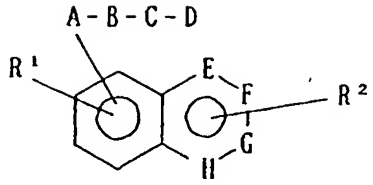
Accordingly, the present inventors consider that substances which can suppress the function of the P-glycoprotein so as to interfere with the outflow of anticancer drugs from cancer cells have ability to potentiate the effect of anticancer drugs and are particularly effective in overcoming drug resistance and thus make promising novel cancer chemotherapeutics.

In fact, Tsuruo et al. found that calcium antagonists such as verapamil prevent discharge of anticancer drugs from cancer cells and that, accordingly with the use of these calcium antagonists in combination, the effect of anticancer drugs such as adriamycin and vincristine on drug-resistant cancer cells is reinforced in vitro and in vivo. However, in the case where these calcium antagonists are used clinically for cancer patients, side effects such as hypotonia and arhythmia occur, which creates another serious problem in cancer chemotherapy. Consequently, drugs which have a stronger potentiating activity for anticancer drugs against drug-resistant cancers and manifest fewer side effects are desired.

EP-A-229 623 concerns compounds with calcium antagonist activity. Example 33 thereof is a compound according to formula (I) below, except that the group 'I' represents $-(CH_2)_3-$.

As a result of intensive investigations in view of above-mentioned problems, the present inventors found that certain compounds manifest strong activity to potentiate the effects of anticancer drugs when used against drug-resistant cancer and have low toxicity and fewer side effects, and thus completed the present invention.

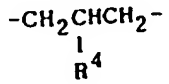
The present invention concerns compounds within the following general formula [I] and salts thereof (hereinafter referred to as the compounds according to the present invention) and to therapeutic compositions to potentiate the effect of anticancer drugs containing the compounds according to the present invention as active ingredients:



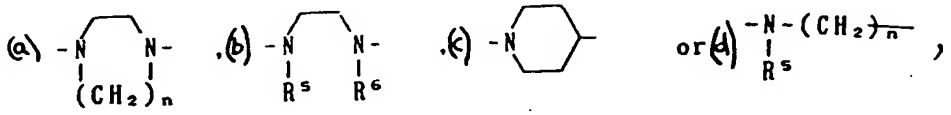
[I]

(I)

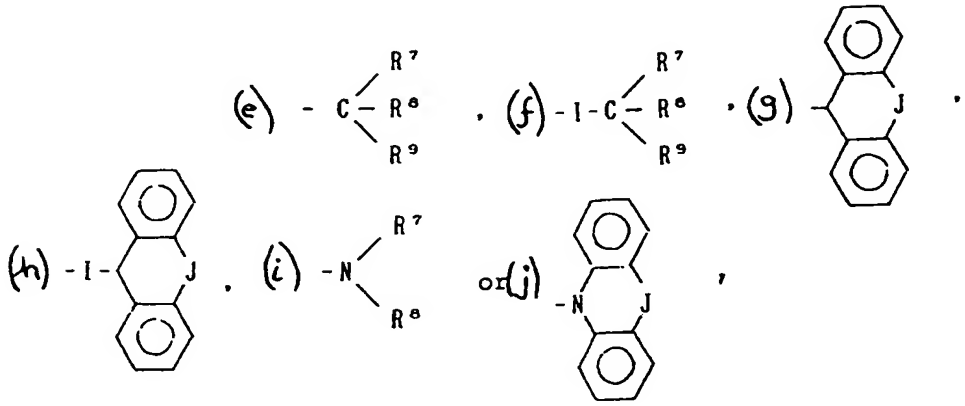
in which A represents an oxygen or sulfur atom or a methylene, amino or -NR^3 group, which is bound to any one of the available sites on the condensed benzene ring, B represents -$(CH_2)_n$-,



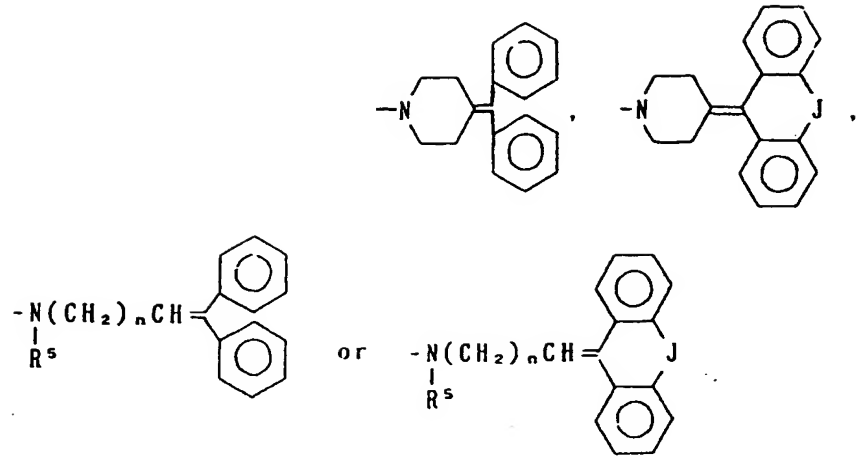
or -$CO(CH_2)_n$-, C represents



D represents



with the proviso that if C is (a) or (b) then D is not (i) or (j) and I is not a nitrogen atom;
or C and D together form



E, F, G and H each independently represent a carbon or nitrogen atom, provided that either one or two of them is nitrogen. R^1 and R^2 each independently represent a hydrogen or halogen atom, a C_{1-4} alkyl, amino group, substituted amino group, a C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylsulfonyl, trifluoromethyl, cyano, nitro, amide or hydroxy group, R^1 and R^2 may be substituted on any of the possible sites on the condensed ring and may be one on each of the two rings of which the condensed ring consists or two at the same time on one of the rings. R^3 represents a hydrogen atom or a C_{1-4} alkyl or acyl group. R^4 represents a hydroxyl, lower alkylamino (where alkyl is C_{1-4}), C_{1-4} alkoxyl or C_{1-2} acyloxy group, R^5 and R^6 each independently represent a hydrogen atom or a C_{1-4} alkyl or hydroxyalkyl group, R^7, R^8 and R^9 each independently represent a hydrogen atom or a hydroxy, phenyl, pyridyl or substituted phenyl group, I represents an oxygen atom,

or a nitrogen atom,

J represents $-(CH_2)_m-$, $-CH=CH-$, $-OCH_2-$ or an oxygen atom, n represents an integral number in the range between 1 and 10, and m represents an integral number, 0, 1 or 2.

Preferred embodiments of the present invention significantly suppress the outflow of anticancer drugs from cancer cells and, moreover, are characterized by their low toxicity and extremely low incidence of side effects to the patient such as hypotonia.

Accordingly, such embodiments of the present invention are effective to facilitate retaining anticancer drugs in cancer cells, which cells are less sensitive or resistant to anticancer drugs, and can thus provide new therapeutic means to advance cancer chemotherapy.

In another aspect the invention provides the use of a compound of general formula [X] in preparing a composition for use in a method of treating cancer which comprises potentiating the effect of an anticancer drug by administering to a patient an effective amount of an anticancer drug independently or in combination with the compound of formula [X]. Formula [X] is the same as formula [I] as defined about except that it also encompasses the possibility that I represents $-(CH_2)_n-$.

DETAILED DESCRIPTION AND THE PREFERRED EMBODIMENTS

As used herein, the terms used above have the following meanings: a halogen atom means a fluorine atom, chlorine atom, bromine atom or iodine atom.

A lower alkyl group means a methyl group, ethyl group, propyl group, or butyl group, including their positional isomers.

A substituted amino group means, for example, a methylamino group, dimethylamino group, ethylamino group, diethylamino group, propylamino group, or butylamino group.

A lower alkoxy group means a methoxy group, ethoxy group, propoxy group, or butoxy group.

An amido group means, for example, a formamido group, acetamido group, or benzamido group.

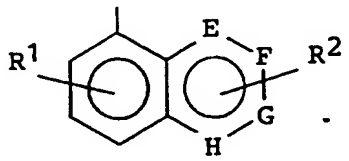
An acyl group means, for example, a formyl group, acetyl group, propanoyl group, or benzoyl group.

An acyloxy group means, for example, a formyloxy group or acetoxy group

A hydroxyalkyl group means, for example, a 2-hydroxyethyl group, 2-hydroxypropyl group or 3-hydroxypropyl group.

A substituted phenyl group means, for example, a halogenophenyl group, alkoxyphenyl group, aminophenyl group, alkylaminophenyl group, acylaminophenyl group, or hydroxyphenyl group which is substituted at the 2-, 3- or 4-position.

Examples of a partial structure of the general formula (I) represented by the formula



include 2-methylquinoline, 3-methylquinoline, 4-methylquinoline, 6-methylquinoline, 7-methylquinoline, 8-methylquinoline, 2-ethylquinoline, 3-ethylquinoline, 4-ethylquinoline, 6-ethylquinoline, 7-ethylquinoline, 8-ethylquinoline, 2,4-dimethylquinoline, 2,4-diethylquinoline, 7-nitroquinoline, 8-nitroquinoline, 2-methoxyquinoline, 3-methoxyquinoline, 4-methoxyquinoline, 6-methoxyquinoline, 7-methoxyquinoline, 8-methoxyquinoline, 2-chloroquinoline, 3-chloroquinoline, 4-chloroquinoline, 6-chloroquinoline, 7-chloroquinoline, 8-chloroquinoline, 2-trifluoromethylquinoline, 3-trifluoromethylquinoline, 4-trifluoromethylquinoline, 6-trifluoromethylquinoline, 7-trifluoromethylquinoline, 8-trifluoromethylquinoline, 2,4-bis(trifluoromethyl)-quinoline, 2-fluoroquinoline, 3-fluoroquinoline, 4-fluoroquinoline, 6-fluoroquinoline, 7-fluoroquinoline, 8-fluoroquinoline, 2-bromoquinoline, 3-bromoquinoline, 4-bromoquinoline, 6-bromoquinoline, 7-bromoquinoline, 8-bromoquinoline, 2-iodoquinoline, 8-iodoquinoline, 2-propylquinoline, 3-propylquinoline, 2,4-dipropyl-quinoline, 8-propylquinoline, 2-butylquinoline, 8-butylquinoline, 2,4-dibutylquinoline, 2-aminoquinoline, 7-aminoquinoline, 8-aminoquinoline, 2-methylaminoquinoline, 7-methylaminoquinoline, 8-methylaminoquinoline, 2-dimethylaminoquinoline, 7-dimethylamoinoquinoline, 8-dimethylaminoquinoline, 2-ethylaminoquinoline, 8-ethylaminoquinoline, 2-diethylaminoquinoline, 8-diethylaminoquinoline, 2-propylaminoquinoline, 8-propylaminoquinoline, 2-ethoxyquinoline, 7-ethoxyquinoline, 8-ethoxyquinoline, 2-propoxyquinoline, 7-propoxyquinoline, 2-butoxyquinoline, 8-butoxyquinoline, 2-cyanoquinoline, 2-formamidoquinoline, 2-acetamidoquinoline, 7-acetamidoquinoline, 8-acetamidequinoline, 3-hydroxyquinoline, 7-hydroxyquinoline, 8-hydroxyquinoline, isoquinoline, quinoxaline, quinazoline and cinnoline.

Examples of A, which is a partial structure of the general formula (I), include an oxygen atom -O-, sulfur atom -S-, methylene group -CH_2-, amino group -NH-, methylamino group -N(CH_3)-, ethylamino group -N(CH_2CH_3)-, propylamino group -N($CH_2CH_2CH_3$)-, butylamino group -N($CH_2CH_2CH_2CH_3$)-, acetylamino group -N($COCH_3$)-, formylamino group -N(CHO)-, propanoylamino group -N($COCH_2CH_3$)- and benzoylamino group -N(COPh)-.

Examples of B, which is also a partial structure of the general formula (I), include -CH_2CH_2-, -$CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2$-, -$CH_2CH(OH)CH_2$-, -$CH_2CH(OCOCH_3)CH_2$-, -$CH_2CH(OCHO)CH_2$-, -$CH_2CH(NH_2)CH_2$-, -$CH_2CH(NHCH_3)CH_2$-, -$CH_2CH(NMe_2)CH_2$-, -$CH_2CH(NHCH_2CH_3)CH_2$-, -$CH_2CH(OCH_3)CH_2$-, -$CH_2CH(OCH_2CH_3)CH_2$-, -$COCH_2CH_2$-, -$COCH_2CH_2CH_2$- and -$COCH_2CH_2CH_2CH_2$-.

Examples of C, which also is a partial structure of the general formula (I), include a piperazine ring, homopiperazine ring, N,N'-dimethylethylenediamine, N,N'-diethylethylenediamine, ethylamine, propylamine, N-methylpropylamine and a piperidine ring.

Examples of D, which is also a partial structure of the general formula (I), include a diphenylmethyl group, benzyl group, (4-pyridyl)methyl group, (3-pyridyl)methyl group, (2-pyridyl)methyl group, phenyl-(2-pyridyl)methyl group, phenyl-(3-pyridyl)methyl group, phenyl-(4-pyridyl)methyl group, di(2-pyridyl)methyl group, di(4-pyridyl)methyl group, diphenyl-hydroxymethyl group, triphenylmethyl group, (4-chlorophenyl)-phenylmethyl group, bis(4-chlorophenyl)methyl group, (4-fluorophenyl)-phenylmethyl group, bis(4-fluorophenyl)methyl group, (4-methoxyphenyl)-phenylmethyl group, bis(4-methoxyphenyl)methyl group, (4-hydroxyphenyl)-phenylmethyl group, bis(4-hydroxyphenyl)methyl group, (4-dimethylaminophenyl)-phenylmethyl group, (2,3-dimethoxyphenyl)-(3,4-dimethoxyphenyl)methyl group, bis(4-dimethylaminophenyl)-methyl group, 5-fluorenyl group, 9,10-dihydro-9-anthrasenyl group, 5-dibenzosuberanyl group, 6,11-dihydrodibenzo[b,e]oxepine-11-yl group, 5-dibenzosuberenyl group, 5-xanthenyl group, diphenylmethoxy

group, 5-dibenzosuberanyloxy group, phenyl-(2-pyridyl)methoxy group, phenyl-(3-pyridyl)methoxy group, phenyl-(4-pyridyl)methoxy group, di(2-pyridyl)methoxy group, di(3-pyridyl)methoxy group, di(4-pyridyl)-methoxy group, bis(4-methoxyphenyl)methoxy group, bis(4-hydroxyphenyl)methoxy group, bis(4-dimethylaminophenyl)methoxy group, (2,3-dimethoxyphenyl)-(3,4-dimethoxyphenyl)methoxy group, 6,11-dihydrodibenzo[b,e]oxepine-11-yloxy group, 5-dibenzosuberenyloxy group, 5-xanthenyloxy group, 2,2-diphenylethyl group, 2,2-di(2-pyridyl)ethyl group, 2,2-di(4-pyridyl)ethyl group, 2-phenyl-2-(2-pyridyl)ethyl group, 2-phenyl-2-(3-pyridyl)ethyl group, 2-phenyl-2-(4-pyridyl)ethyl group, 2,2-diphenyl-2-hydroxyethylgroup, 2-(4-chlorophenyl)-2-phenylethyl group, 2,2-bis(4-chlorophenyl)ethyl group, 2-(4-methoxyphenyl)-2-phenylethyl group, 2,2-bis(4-methoxyphenyl)ethyl group, 2-(4-hydroxyphenyl)-2-phenylethyl group, 2,2-bis(4-hydroxyphenyl)ethyl group, 2-(4-dimethylaminophenyl)-2-phenylethyl group, 2-(2,3-dimethoxyphenyl)-2-(3,4-dimethoxypheny)ethyl group, (5-dibenzosuberanyl)methyl group, 2,2-diphenylacetyl group, 2-phenylacetyl group, 2-(4-pyridyl)acetyl group, 2-(3-pyridyl)acetyl group, 2-(2-pyridyl)acetyl group, 2-phenyl-2-(2-pyridyl)acetyl group, 2-phenyl-2-(3-pyridyl)acetyl group, 2-phenyl-2-(4-pyridyl)acetyl group, 2,2-di(2-pyridyl)acetyl group, 2,2-di(4-pyridyl)acetyl group, 2,2,2-triphenylacetyl group, 2-(4-chlorophenyl)-2-phenylacetyl group, 2,2-bis(4-chlorophenyl)acetyl group, 2-(4-fluorophenyl)-2-phenylacetyl group, 2,2-bis(4-fluorophenyl)acetyl group, 2-(4-methoxyphenyl)-2-phenylacetyl group, 2,2-bis(4-methoxyphenyl)acetyl group, 2-(4-hydroxyphenyl)-2-phenylacetyl group, 2,2-bis(4-hydroxyphenyl)acetyl group, 2-(4-dimethylaminophenyl)-2-phenylacetyl group, 2,2-bis(4-dimethylaminophenyl)acetyl group, 2-(2,3-dimethoxyphenyl)-2-(3,4-dimethoxyphenyl)acetyl group, dibenzosuberane-5-carbonyl group, fluorene-5-carbonyl group, 6,11-dihydrobenzo[b,e]oxepine-11-carbonyl group, dibenzosuberene-5-carbonyl group, 5-xanthenecarbonyl group, 3,3-diphenylpropyl group, 3-(dibenzosuberane-5-yl)ethyl group, (diphenylmethyl)amino group, 5-dibenzosuberanylamino group, N,N-diphenylamino group, N-phenyl-N-(2-pyridyl)amino group, N-phenyl-N-(3-pyridyl)amino group, N-phenyl-N-(4-pyridyl)amino group, N,N-bis(4-chlorophenyl)amino group, N,N-bis(4-fluorophenyl)amino group, N,N-bis(4-methoxyphenyl)amino group, N,N-bis(4-hydroxyphenyl)-amino group, 9,10-dihydroacridine-10-yl group, 10,11-dihydro-dibenzo[b,f]azepine-5-yl group, dibenzo[b,f]-azepine-5-yl group, N,N-diphenylcarbamoyl group, N-phenyl-N-(2-pyridyl)carbamoyl group, N-phenyl-N-(3-pydidyl)carbamoyl group, N-phenyl-N-(4-pydidyl)carbamoyl group, N,N-bis(4-chlorophenyl)carbamoyl group, N,N-bis(4-fluorophenyl)carbamoyl group, N,N-bis(4-methoxyphenyl)carbamoyl group, N,N-bis(4-hydroxyphenyl)carbamoyl group, 9,10-dihydroacridine-10-carbonyl group, 10,11-dihydro-dibenzo[b,f]-azepine-5-carbonyl group, dibenzo[b,f]azepine-5-carbonyl group and diphenylmethylene group.

Specific examples of compounds represented by general formula (I) include:

5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxylpropoxy]quinoline,
5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxylpropoxy]quinoline,
5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxylpropoxy]-2-methylquinoline,
5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxylpropoxy]-3-methylquinoline,
5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxylpropoxy]-4-methylquinoline,
5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxylpropoxy]-6-methylquinoline,
5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxylpropoxy]-7-methylquinoline,
5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxylpropoxy]-8-methylquinoline,
5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxylpropoxy]-2-methylquinoline,
5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxylpropoxy]-3-methylquinoline,
5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxylpropoxy]-4-methylquinoline,
5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxylpropoxy]-6-methylquinoline,
5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxylpropoxy]-7-methylquinoline,
5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxylpropoxy]-8-methylquinoline,
5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxylpropoxy]-2-methoxyquinoline,
5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxylpropoxy]-3-methoxyquinoline,
5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxylpropoxy]-4-methoxyquinoline,
5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxylpropoxy]-6-methoxyquinoline,
5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxylpropoxy]-7-methoxyquinoline,
5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxylpropoxy]-8-methoxyquinoline,
5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxylpropoxy]-2-methoxyquinoline,
5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxylpropoxy]-3-methoxyquinoline,
5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxylpropoxy]-4-methoxyquinoline,
5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxylpropoxy]-6-methoxyquinoline,
5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxylpropoxy]-7-methoxyquinoline,
5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxylpropoxy]-8-methoxyquinoline,
2-ethyl-5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxylpropoxy]quinoline,

2-ethyl-5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxylpropoxy]quinoline,
5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxylpropoxy]-2-propylquinoline,
5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxylpropoxy]-2-propylquinoline,
2-butyl-5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxylpropoxy]quinoline,
2-butyl-5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxylpropoxy]quinoline,
2,4-dimethyl-5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxylpropoxy]quinoline,
2,4-dimethyl-5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxylpropoxy]quinoline,
5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxylpropoxy]-7-nitroquinoline,
5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxylpropoxy]-8-nitroquinoline,
5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxylpropoxy]-7-nitroquinoline,
5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxylpropoxy]-8-nitroquinoline,
2-chloro-5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxylpropoxy]quinoline,
3-chloro-5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxylpropoxy]quinoline,
4-chloro-5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxylpropoxy]quinoline,
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2-chloro-5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxylpropoxy]quinoline,
3-chloro-5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxylpropoxy]quinoline,
4-chloro-5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxylpropoxy]quinoline,
6-chloro-5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxylpropoxy]quinoline,
7-chloro-5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxylpropoxy]quinoline,
8-chloro-5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxylpropoxy]quinoline,
5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxylpropoxy]-2-trifluoromethylquinoline,
5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxylpropoxy]-4-trifluoromethylquinoline,
5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxylpropoxy]-2-trifluoromethylquinoline,
5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxylpropoxy]-4-trifluoromethylquinoline,
2,4-bis(trifluoromethyl)-5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxylpropoxy]quinoline,
2,4-bis(trifluoromethyl)-5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxylpropoxy]quinoline,
5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxylpropoxy]-2-fluoroquinoline,
5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxylpropoxy]-4-fluoroquinoline,
5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxylpropoxy]-2-fluoroquinoline,
5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxylpropoxy]-4-fluoroquinoline,
2-bromo-5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxylpropoxy]quinoline,
3-bromo-5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxylpropoxy]quinoline,
4-bromo-5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxylpropoxy]quinoline,
2-bromo-5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxylpropoxy]quinoline,
3-bromo-5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxylpropoxy]quinoline,
4-bromo-5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxylpropoxy]quinoline,
2-amino-5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxylpropoxy]quinoline,
2-amino-5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxylpropoxy]quinoline,
5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxylpropoxy]-2-methylaminoquinoline,
5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxylpropoxy]-2-methylaminoquinoline,
2-dimethylamino-5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxylpropoxy]quinoline,
2-dimethylamino-5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxylpropoxy]quinoline,
2-ethoxy-5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxylpropoxy]quinoline,
2-ethoxy-5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxylpropoxy]quinoline,
2-cyano-5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxylpropoxy]quinoline,
2-cyano-5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxylpropoxy]quinoline,
5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxylpropoxy]-8-hydroxyquinoline,
5[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxylpropoxy]-8-hydroxyquinoline,
5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxylpropylthio]quinoline,
5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxylpropylthio]quinoline,
5-[4-(4-diphenylmethylpiperazine-1-yl)butyl]quinoline,
5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)butyl]quinoline,
5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxypropylamino]quinoline,
5[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxypropylamino]quinoline,
N-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxypropyl]-N-methyl-5-quinolineamine,

N-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxypropyl]-N-methyl-5-quinolineamine,
N-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxypropyl]-N-acetyl-5-quinolineamine,
N-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxypropyl]-N-acetyl-5-quinolineamine,
5-[2-(4-diphenylmethylpiperazine-1-yl)ethoxy]quinoline,
5-[2-(4-(dibenzosuberane-5-yl)piperazine-1-yl)ethoxy]quinoline,
5-[4-(4-diphenylmethylpiperazine-1-yl)butoxy]quinoline,
5-[4-(4-(dibenzosuberane-5-yl)piperazine-1-yl)butoxy]quinoline,
5-[3-(4-diphenylmethylpiperazine-1-yl)propoxy]quinoline,
5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)propoxy]quinoline,
5-[2-acetoxy-3-(4-diphenylmethylpiperazine-1-yl)propoxy]quinoline,
5-[2-acetoxy-3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)propoxy]quinoline,
5-[2-amino-3-(4-diphenylmethylpiperazine-1-yl)propoxy]quinoline,
5-[2-amino-3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)propoxy]quinoline,
5-[3-(4-diphenylmethylpiperazine-1-yl)-2-methylaminopropoxy]quinoline,
5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-methylaminopropoxy]quinoline,
5-[3-(4-diphenylmethylpiperazine-1-yl)-2-methoxypropoxy]quinoline,
5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-methoxypropoxy]quinoline,
5-[3-(4-diphenylmethylpiperazine-1-yl)-2-propionamido]quinoline,
5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)propionamido]quinoline,
5-[3-(4-diphenylmethylpiperazine-1-yl)-N-methylpropionamido]quinoline,
5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-N-propionamido]quinoline,
5-[3-(4-diphenylmethylhomopiperazine-1-yl)-2-hydroxypropoxy]quinoline,
5-[3-(4-(dibenzosuberane-5-yl)homopiperazine-1-yl)-2-hydroxypropoxy]quinoline,
5-(3-[N-(2-(N-diphenylmethyl-N-methylamino)ethyl)-N-methylamino]-2-hydroxypropoxy)quinoline,
5-(3-(N-[2-(N-(dibenzosuberane-5-yl)-N-methylamino)ethyl]-N-methylamino)-2-hydroxypropoxy)quinoline,
5-[3-(4-(diphenyl-hydroxymethyl)piperidine-1-yl)-2-hydroxypropoxy]quinoline,
5-[3-(4-(diphenylmethylene)piperidine-1-yl)-2-hydroxypropoxy]quinoline,
5-[3-(4-diphenylmethylpiperidine-1-yl)-2-hydroxypropoxy]quinoline,
5-[3-(4-(diphenyl-hydroxymethyl)piperidine-1-yl)-2-hydroxypropoxy]-2-quinoline,
5-[3-(4-(phenyl-2-pyridylmethyl)piperazine-1-yl)-2-hydroxypropoxy]quinoline,
5-[3-(4-(phenyl-3-pyridylmethyl)piperazine-1-yl)-2-hydroxypropoxy]quinoline,
5-[3-(4-(phenyl-4-pyridylmethyl)piperazine-1-yl)-2-hydroxypropoxy]quinoline,
5-(3-[4-(di-(2-pyridyl)methyl)piperazine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(di-(3-pyridyl)methyl)piperazine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(di-(4-pyridyl)methyl)piperazine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(bis(4-chlorophenyl)methyl)piperazine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(bis(4-fluorophenyl)methyl)piperazine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-((4-chlorophenyl)-phenylmethyl)piperazine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(bis(4-methoxyphenyl)methyl)piperazine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(bis(4-hydroxyphenyl)methyl)piperazine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(bis(4-dimethylaminophenyl)methyl)piperazine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-((2,3-dimethylphenyl)-(3,4-dimethoxyphenyl)methyl)piperazine-1-yl]-2-hydroxypropoxy)quinoline,
5-[3-(4-(fluorene-5-yl)piperazine-1-yl)-2-hydroxypropoxy]quinoline,
5-[3-(4-(9,10-dihydro-9-anthracenyl)piperazine-1-yl)-2-hydroxypropoxy]quinoline,
5-[3-(4-(6,11-dihydrodibenzo[b,e]oxepine-11-yl)piperazine-1-yl)-2-hydroxypropoxy]quinoline,
5-[3-(4-(dibenzosuberene-5-yl)piperazine-1-yl)-2-hydroxypropoxy]quinoline,
5-[3-(4-(xanthene-5-yl)piperazine-1-yl)-2-hydroxypropoxy]quinoline,
5-[3-(4-(diphenylmethoxy)piperidine-1-yl)-2-hydroxypropoxy]quinoline,
5-[3-(4-(dibenzosuberane-5-yloxy)piperazine-1-yl)-2-hydroxypropoxy]quinoline,
5-[3-(4-(phenyl-2-pyridylmethoxy)piperidine-1-yl)-2-hydroxypropoxy]quinoline,
5-[3-(4-(phenyl-3-pyridylmethoxy)piperidine-1-yl)-2-hydroxypropoxy]quinoline,
5-[3-(4-(phenyl-4-pyridylmethoxy)piperidine-1-yl)-2-hydroxypropoxy]quinoline,
5-(3-[4-(di(2-pyridyl)methoxy)piperidine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(di(3-pyridyl)methoxy)piperidine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(di(4-pyridyl)methoxy)piperidine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(bis(4-chlorophenyl)methoxy)piperidine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(bis(4-fluorophenyl)methoxy)piperidine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-((4-chlorophenyl)-phenylmethoxy)piperidine-1-yl]-2-hydroxypropoxy)quinoline,

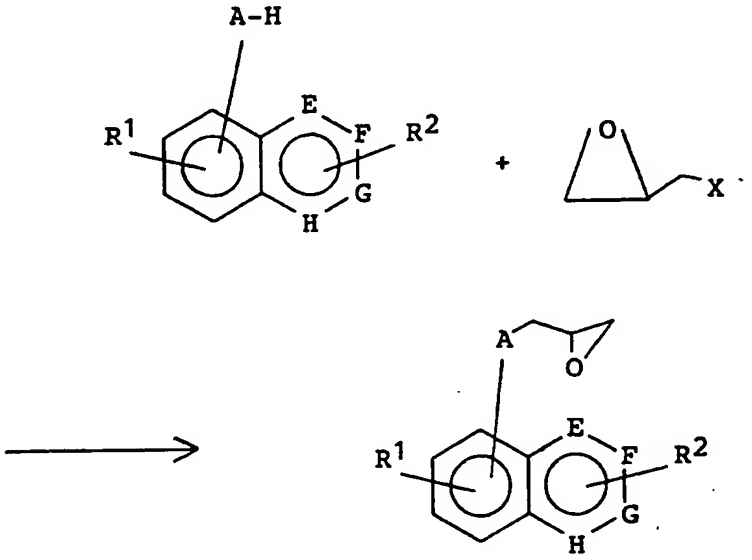
5-(3-[4-(bis(4-methoxyphenyl)-methoxy)piperidine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(bis(4-methoxyphenyl)methoxy)piperidine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(bis(4-dimethylaminophenyl)methoxy)piperidine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-((2,3-dimethoxyphenyl)-(3,4-dimethoxyphenyl)methoxy)piperidine-1-yl]-2-hydroxypropoxy)-quinoline,
5-(3-[4-(9,10-dihydro-9-anthracenyloxy)piperidine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(6,11-dihydrodibenzo[b,e]oxepine-11-yloxy)piperidine-1-yl]-2-hydroxypropoxy)quinoline,
5-[3-(4-(dibenzosuberene-5-yloxy)piperidine-1-yl)-2-hydroxypropoxy]quinoline,
5-[3-(4-(xanthene-5-yloxy)piperidine-1-yl)-2-hydroxypropoxy]quinoline,
5-[3-(4-(2,2-diphenylethyl)piperazine-1-yl)-2-hydroxypropoxy]quinoline,
5-[3-(4-(dibenzosuberane-5-yl)methylpiperazine-1-yl)-2-hydroxypropoxy]quinoline,
5-(3-[4-(2-phenyl-2-(2-pyridyl)ethyl)piperazine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(2-phenyl-2-(3-pyridyl)ethyl)piperazine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(2-phenyl-2-(4-pyridyl)ethyl)piperazine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(2,2-di(2-pyridyl)ethyl)piperazine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(2,2-di(3-pyridyl)ethyl)piperazine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(2,2-di(4-pyridyl)ethyl)piperazine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(2,2-bis(4-chlorophenyl)ethyl)piperazine-1-yl]-2 hydroxypropoxy)quinoline,
5-(3-[4-(2,2-bis(4-fluorophenyl)ethyl)piperazine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(2,2-(4-chlorophenyl)-phenylethyl)piperazine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(2,2-bis(4-methoxyphenyl)ethyl)piperazine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(2,2-bis(4-hydroxyphenyl)ethyl)piperazine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(2,2-bis(4-dimethylaminophenyl)ethyl)piperazine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(2-(2,3-dimethoxyphenyl)-2-(3,4-dimethoxyphenyl)ethyl)piperazine-1-yl]-2-hydroxypropoxy)-quinoline,
5-(3-[4-(fluorene-5-yl)methylpiperazine-1-yl]-2-hydroxypropoxy)quinoline
5-(3-[4-(9,10-dihydro-9-anthracenyl)methylpiperazine-1-yl]-2-hydroxypropoxy)quinoline,
5-[3-(4-(6,11-dihydrodibenzo[b,e]oxepine-11-yl)methylpiperazine-1-yl)-2-hydroxypropoxy]quinoline,
5-[3-(4-(dibenzosuberene-5-yl)methylpiperazine-1-yl)-2-hydroxypropoxy]quinoline,
5-[3-(4-(xanthene-5-yl)methylpiperazine-1-yl)-2-hydroxypropoxy]quinoline,
5-[3-(4-(diphenylacetyl)piperidine-1-yl)-2-hydroxypropoxy]quinoline,
5-[3-(4-(dibenzosuberane-5-carbonyl)piperidine-1-yl)-2-hydroxypropoxy]quinoline,
5-(3-[4-(phenyl-2-pyridylacetyl)piperidine-1-yl)-2-hydroxypropoxy]quinoline,
5-(3-[4-(phenyl-3-pyridylacetyl)piperidine-1-yl)-2-hydroxypropoxy]quinoline,
5-(3-[4-(phenyl-4-pyridylacetyl)piperidine-1-yl)-2-hydroxypropoxy]quinoline,
5-(3-[4-(di-(2-pyridyl)acetyl)piperidine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(di-(3-pyridyl)acetyl)piperidine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(di-(4-pyridyl)acetyl)piperidine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(bis(4-chlorophenyl)acetyl)piperidine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(bis(4-fluorophenyl)acetyl)piperidine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-((4-chlorophenyl)-phenylacetyl)piperidine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(bis(4-methoxyphenyl)acetyl)piperidine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(bis(4-hydroxyphenyl)acetyl)piperidine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(bis(4-dimethylaminophenyl)acetyl)piperidine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-((2,3-dimethoxyphenyl)-(3,4-dimethoxyphenyl)acetyl)piperidine-1-yl]-2-hydroxypropoxy)quinoline,
5-[3-(4-(9,10-dihydro-anthracenyl-9-carbonyl)piperidine-1-yl)-2-hydroxypropoxy]quinoline,
5-(3-[4-(6,11-dihydrodibenzo[b,e]oxepine-11-carbonyl)piperidine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(dibenzosuberene-5-carbonyl)piperidine-1-yl]-2-hydroxypropoxy)quinoline,
5-[3-(4-(xanthene-5-carbonyl)piperidine-1-yl)-2-hydroxypropoxy]quinoline,
5-[3-(4-(2,2-diphenylacetyl)piperazine-1-yl)-2-hydroxypropoxy]quinoline,
5-[3-(4-(dibenzosuberane-5-carbonyl)piperazine-1-yl)-2-hydroxypropoxy]quinoline,
5-(3-[4-(2-phenyl-2-(2-pyridyl)acetyl)piperazine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(2-phenyl-2-(3-pyridyl)acetyl)piperazine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(2-phenyl-2-(4-pyridyl)acetyl)piperazine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(2,2-di-(2-pyridyl)acetyl)piperazine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(2,2-di(3-pyridyl)acetyl)piperazine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(2,2-di(4-pyridyl)acetyl)piperazine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(2,2-bis(4-chlorophenyl)acetyl)piperazine-1-yl]-2-hydroxypropoxy)quinoline,

5-(3-[4-(2,2-bis(4-fluorophenyl)acetyl)piperazine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(2-(4-chlorophenyl)-2-phenylacetyl)piperazine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(2,2-bis(4-methoxyphenyl)acetyl)piperazine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(2,2-bis(4-hydroxyphenyl)acetyl)piperazine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(2,2-bis(4-dimethylaminophenyl)acetyl)piperazine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(2-(2,3-dimethoxyphenyl)-2-(3,4-dimethoxyphenyl)acetyl)piperazine-1-yl]-2-hydroxypropoxy)-quinoline,
5-[3-(4-(fluorene-5-carbonyl)piperazine-1-yl)-2-hydroxypropoxy]quinoline,
5-[3-(4-(9,10-dihydroanthracenyl-9-carbonyl)piperazine-1-yl)-2-hydroxypropoxy]quinoline,
5-[3-(4-(6,11-dihydrodibenzo[b,e]oxepine-11-carbonyl)piperazine-1-yl)-2-hydroxypropoxy]quinoline,
5-[3-(4-(dibenzosuberene-5-carbonyl)piperazine-1-yl)-2-hydroxypropoxy]quinoline,
5-[3-(4-(xanthene-5-carbonyl)piperazine-1-yl)-2-hydroxypropoxy]quinoline,
5-[3-(4-(3,3-diphenylpropyl)piperazine-1-yl)-2-hydroxypropoxy]quinoline,
5-(3-[4-(2-(5-dibenzosuberanyl)ethyl)piperazine-1-yl]-2-hydroxypropoxy)quinoline,
5-[3-(4-(diphenylmethylamino)piperidine-1-yl)-2-hydroxypropoxy]quinoline,
5-(3-[4-((5-dibenzosuberanyl)amino)piperidine-1-yl]-2-hydroxypropoxy)quinoline,
5-[3-(4-(N,N-diphenylamino)piperidine-1-yl)-2-hydroxypropoxy]quinoline,
5-(3-[4-(N-diphenyl-N-(2-pyridyl)amino)piperidine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(N-diphenyl-N-(3-pyridyl)amino)piperidine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(N-phenyl-N-(4-pyridyl)amino)piperidine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(N,N-bis(4-chlorophenyl)amino)piperidine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(N,N-bis(4-fluorophenyl)amino)piperidine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(N,N-bis(4-methoxyphenyl)amino)piperidine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(N,N-bis(4-hydroxyphenyl)amino)piperidine-1-yl]-2-hydroxypropoxy)quinoline,
5-[3-(4-(9,10-dihydroacridine-10-yl)piperidine-1-yl)-2-hydroxypropoxy]quinoline,
5-[3-(4-(10,11-dihydrodibenzo[b,f]azepine-5-yl)piperidine-1-yl)-2-hydroxypropoxy]quinoline,
5-[3-(4-(dibenzo[b,f]azepine-5-yl)piperidine-1-yl)-2-hydroxypropoxy]quinoline,
5-[3-(4-(N,N-diphenylcarbamoyl)piperidine-1-yl)-2-hydroxypropoxy]quinoline,
5-(3-[4-(N-phenyl-N-(2-pyridyl)carbamoyl)piperidine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(N-phenyl-N-(3-pyridyl)carbamoyl)piperidine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(N-phenyl-N-(4-pyridyl)carbamoyl)piperidine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(N,N-bis(4-chlorophenyl)carbamoyl)piperidine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(N,N-bis(4-fluorophenyl)carbamoyl)piperidine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(N,N-bis(4-methoxyphenyl)carbamoyl)piperidine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(N,N-bis(4-hydroxyphenyl)carbamoyl)piperidine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(9,10-dihydroacridine-10-carbonyl)piperidine-1-yl]-2-hydroxypropoxy)quinoline,
5-[3-(4-(10,11-dihydrodibenzo[b,f]azepine-5-carbonyl)piperidine-1-yl)-2-hydroxypropoxy]quinoline,
5-[3-(4-(dibenzo[b,f]azepine-5-carbonyl)piperidine-1-yl)-2-hydroxypropoxy]quinoline,
5-[3-(4-(diphenylmethylene)piperidine-1-yl)-2-hydroxypropoxy]quinoline,
5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxypropoxy]isoquinoline,
5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxypropoxy]isoquinoline,
5-[3-(4-diphenylmethylhomopiperazine-1-yl)-2-hydroxypropoxy]isoquinoline,
8-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxylpropoxy]isoquinoline,
8-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxylpropoxy]quinoline,
5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxylpropoxy]quinoxaline,
5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxylpropoxy]quinazoline,
5-(3-[4-((4-pyridyl)phenylmethyl)piperazine-1-yl]-2-hydroxylpropoxy)quinoline,
2,4-dimethyl-5-[3-((α,α-diphenylacetyl)piperazine-1-yl)-2-hydroxylpropoxy]quinoline,
2-trifluoromethyl-4-methyl-5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxypropoxy]quinoline,
2-trifluoromethyl-4-methyl-5-[3-(4-(α,α-diphenylacetyl)piperazine-1-yl)-2-hydroxypropoxy]quinoline,
2-trifluoromethyl-4-methyl-5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxypropoxy]quinoline,
5-(3-[4-(bis(4-fluorophenyl)methyl)piperazine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-((4-chlorophenyl)-phenylmethyl)piperazine-1-yl]-2-hydroxypropoxy)quinoline,
5-(3-[4-(bis(4-methoxyphenyl)methyl)piperazine-1-yl]-2-hydroxypropoxy)quinoline,
5-[3-(4-(iminodibenzyl-5-carbonyl)piperazine-1-yl)-2-hydroxypropoxy]quinoline,
2,4-dimethyl-5-[3-(4-(iminodibenzyl-5-carbonyl)piperazine-1-yl)-2-hydroxypropoxy]quinoline,
5-[3-(N'-(dibenzosuberane-5-yl)ethylenediamino)-2-hydroxypropoxy]quinoline,
5-[3-(N,N'-dimethyl-N'-(dibenzosuberane-5-yl)ethylenediamino)-2-hydroxypropoxy]quinoline,

2-methylthio-5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxypropoxy]quinoline,
2-methylthio-5-[3-(4-(α,α-diphenylacetyl)piperazine-1-yl)-2-hydroxypropoxy]quinoline,
2,4-dimethyl-5-[3-(N,N'-dimethyl-N'-(dibenzosuberane-5-yl)ethylenediamino)-2-hydroxypropoxy]-quinoline,
2,4-dimethyl-5-[3-(4-diphenylmethylenepiperidine-1-yl)-2-hydroxypropoxy]quinoline,
5-[3-(10,11-dihydro-N-methyl-5H-dibenzo[a,d]-cycloheptene-$\Delta^{5,7}$-propylamino)-2-hydroxypropoxy]-quinoline,
5-[3-(3,3-diphenylpropylamino)-2-hydroxypropoxy]quinoline,
5-[3-(2,2-diphenylethylamino)-2-hydroxypropoxy]quinoline,
2-methylsulfonyl-5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxypropoxy]quinoline,
5-[3-(4-(xanthene-9-yl)piperazine-1-yl)-2-hydroxypropoxy]quinoline,
5-[3-(N-methyl-3-(5-iminobenzyl)propylamino)-2-hydroxypropoxy]quinoline,
5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxypropylthio]quinoline, and
5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxypropylthio]quinoline.

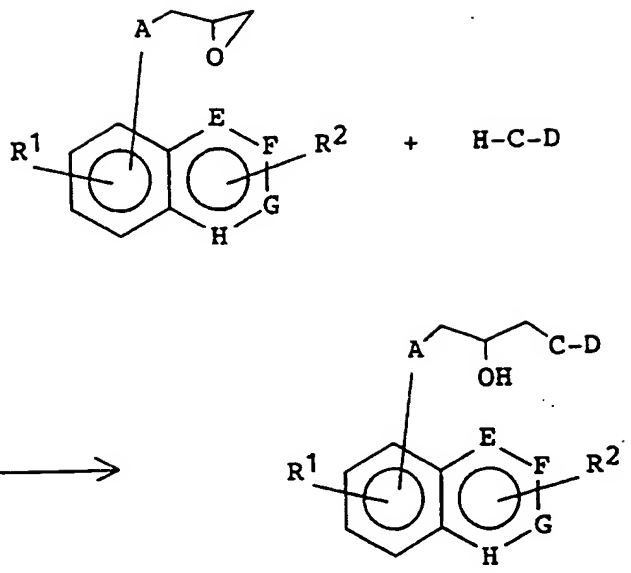
Salts of the compounds according to the present invention include salts of inorganic acids such as hydrochloric acid and sulfuric acid as well as organic salts such as acetic acid, oxalic acid, maleic acid and tartaric acid. Compounds of the present invention have an asymmetic carbon atom in their structure, and therefore optical isomers exist. All of these optical isomers are regarded as within the present invention. The compounds of the present invention are prepared as follows: First synthetic method:

A heterocyclic compound represented by the following formula is reacted with a halide such as epichlorohydrin or epibromohydrin in the presence of a base in a solvent at an appropriate temperature in order to form the corresponding epoxy compound. The above-mentioned base is an inorganic base such as sodium hydroxide, sodium hydride, potassium t-butoxide or sodium carbonate, or an organic base such as triethylamine, pyridine or DBU. The suitable solvent is an aqueous solvent or an organic solvent such as an alcohol, acetone, THF and DMF, and the reaction temperature is preferably in the range of 0 to 100 • C.



where R^1, R^2, A, E, F, G and H are as defined above, and X is a halogen atom.

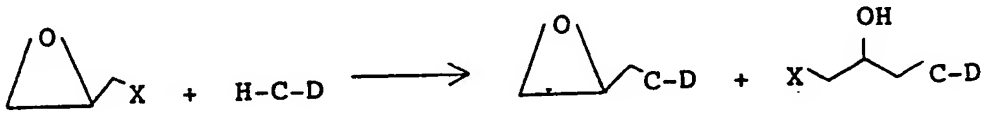
Afterward, the synthesized epoxy compound is thermally reacted with a corresponding amine derivative in a solvent in order to obtain the compound having the general formula (I) wherein B is $-CH_2CH(OH)CH_2-$ of the present invention.



where R^1, R^2, A, E, F, G and H are as defined above.

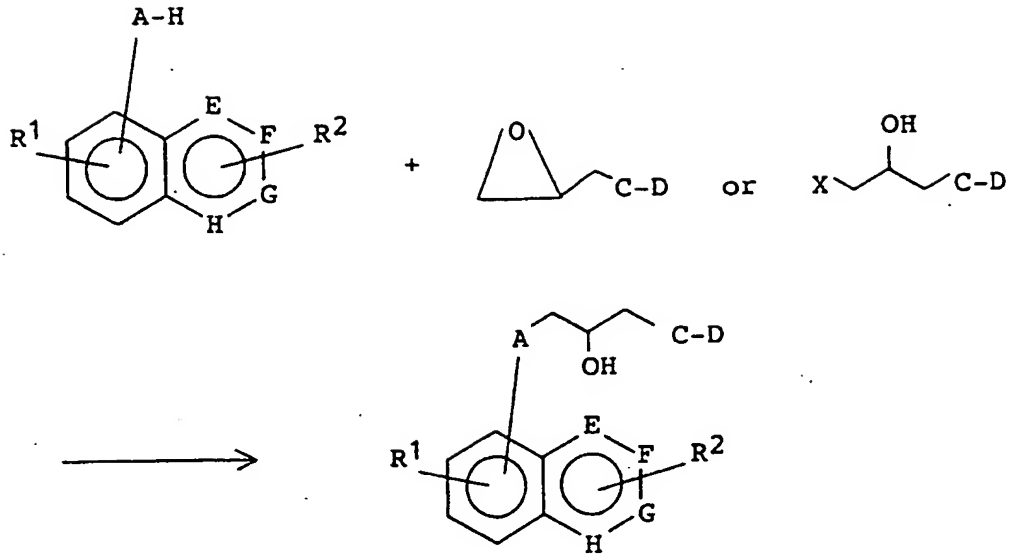
As used above, "thermally" means in the temperature range of from room temperature to a boiling point of the used solvent. The solvent is an organic solvent such as an alcohol, acetone, chloroform or DMF.

A second method of synthesizing the compounds of the present invention is as follows: A halide such as epichlorohydrin or epibromohydrin is reacted with a corresponding amine derivative thermally or in the presence of a base in a solvent in order to form the corresponding epoxy compound and hydroxyhalogen compound.



where X is a halogen, and C and D are as defined above.

Afterward, a heterocyclic compound represented by the following formula is reacted with the above synthesized epoxy compound or hydroxyhalogen compound thermally or in the presence of a base or acid in a solvent in order to obtain the compound having the general formula (I) wherein B is $-CH_2CH(OH)CH_2-$ of the present invention.



where R^1, R^2, A, C, D, E, F, G and H are as defined above, and X is a halogen.

The above-mentioned base is an inorganic base such as sodium hydroxide, sodium hydride, potassium t-butoxide or potassium carbonate, or an organic base such as triethylamine, pyridine or DBU.

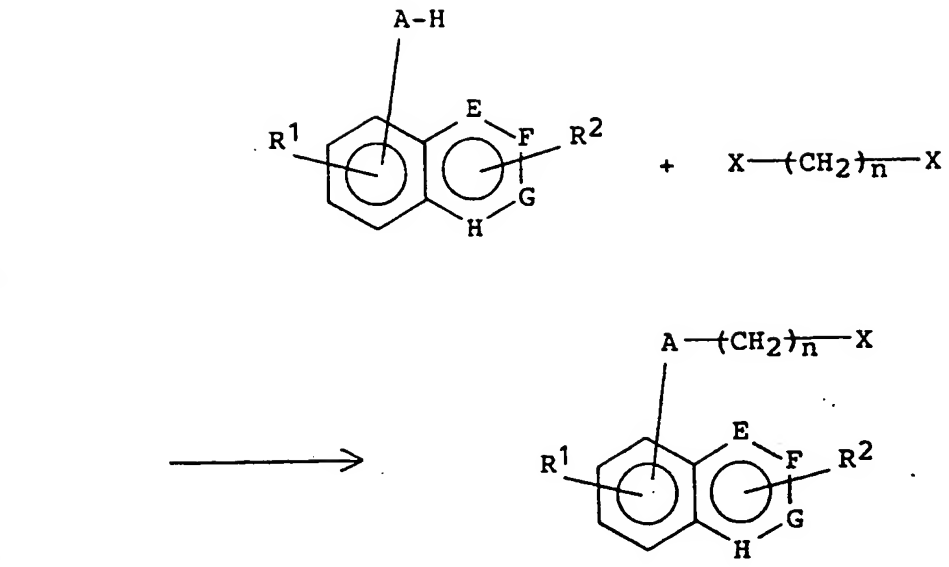
The above-mentioned acid is an organic acid such as tosyl or camphorsulfonic acid, an inorganic acid such as hydrochloric acid or sulfuric acid, or a Lewis acid such as titanium tetrachloride, tin tetrachloride or trimethylsilyl-trifluoromethanesulfonic acid.

The solvent used is an organic solvent such as methylene chloride, acetone, an alcohol, tetrahydrofuran or dimethylformamide. The term "thermally" means "in the temperature range of from room temperature to a boiling point of the solvent".

A third method of synthesizing the compounds of the present invention is as follows: A heterocyclic compound represented by the following formula is reacted with a dihalogenoalkyl material such as 1,2-dibromoethane, 1,3-dibromopropane, 1,3-dichloropropane or 1,4-dibromobutane in the presence of a base in a solvent in order to form the corresponding halogenoalkyl compound.

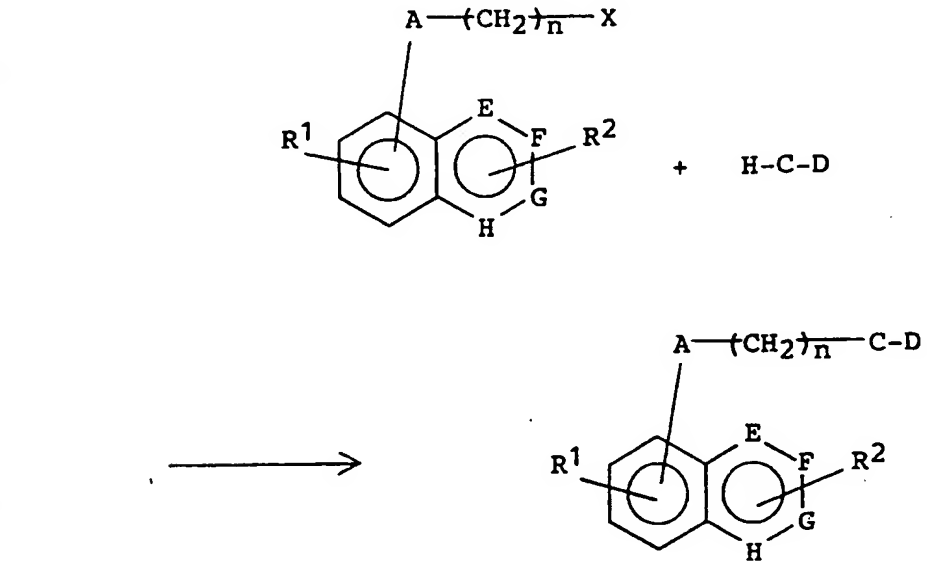
The above-mentioned base is an inorganic salt such as sodium hydroxide, sodium hydride, potassium t-butoxide or sodium carbonate, or an organic base such as triethylamine, pyridine or DBU.

The solvent used is an aqueous solvent or an organic solvent such as an alcohol, acetone, THF or DMF, and the reaction temperature is in the range of from room temperature to a boiling point of the used solvent.



where R^1, R^2, A, E, F, G and H are as defined above, and X is a halogen atom.

Afterward, the synthesized halogenoalkyl compound is reacted with the corresponding amine derivative theremally in a solvent, thereby obtaining a compound having the general formula (I) wherein B is $-(CH_2)_n-$ of the present invention.



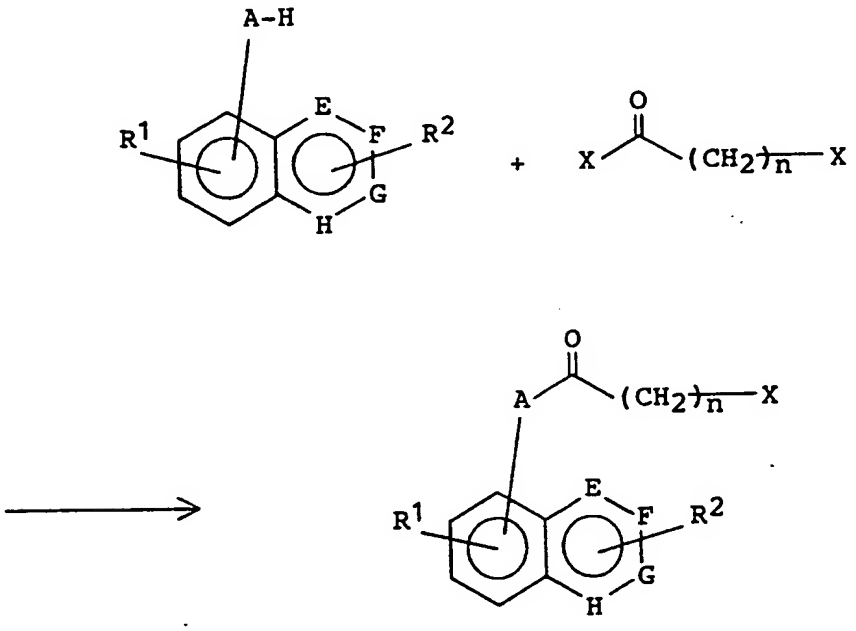
where R^1, R^2, A, C, D, E, F, G and H are as defined above, and X is a halogen atom.

The above-mentioned "thermally" means in the temperature range of from room temperature to a boiling point of the used solvent. The solvent used is an organic solvent such as an alcohol, acetone, chloroform or DMF.

A fouth method of synthesizing compounds of the present invention is as follows: A heterocyclic compound represented by the following formula is reacted with an acid halide such as 3-chloropropionyl chloride, or an acid anhydride theremally or in the presence of a base in a solvent, thereby forming the corresponding halide.

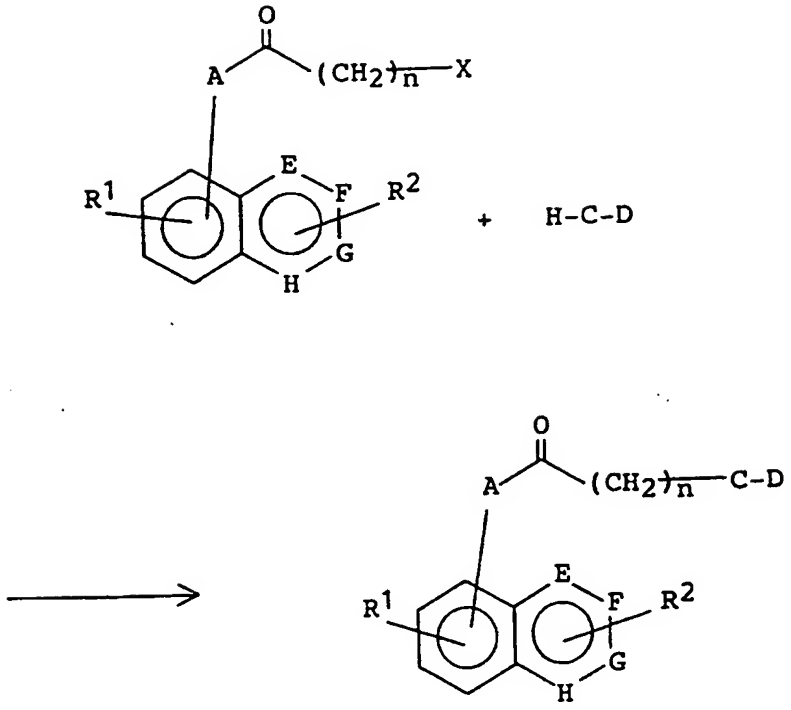
The above-mentioned "thermally" means in the temperature range of from room temperature to a boiling point of the used solvent.

The above-mentioned base is an inorganic base such as sodium hydroxide, sodium hydride or potassium t-butoxide, or an organic base such as triethylamine, pyridine or DBU. The solvent used is an organic solvent such as methylene chloride, chloroform or toluene.



where R^1, R^2, A, E, F, G, H and X are as defined above.

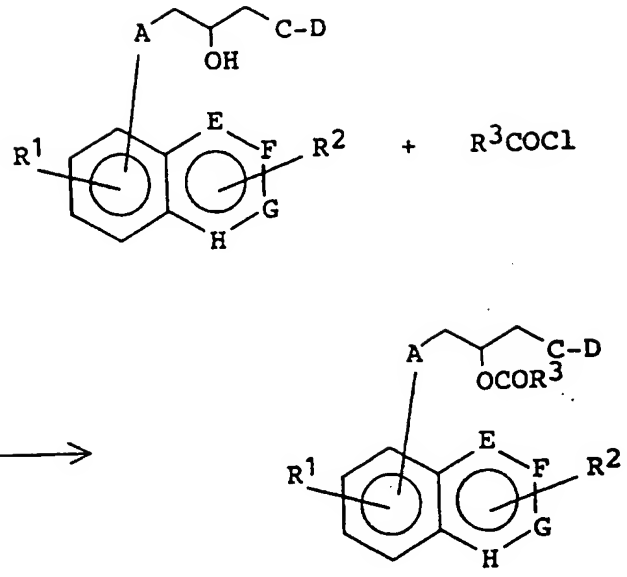
Afterward, the synthesized halide is thermally reacted with a corresponding amine derivative in a solvent in order to obtain a compound having the general formula (I) wherein B is $-CO(CH_2)_n-$ of the present invention.

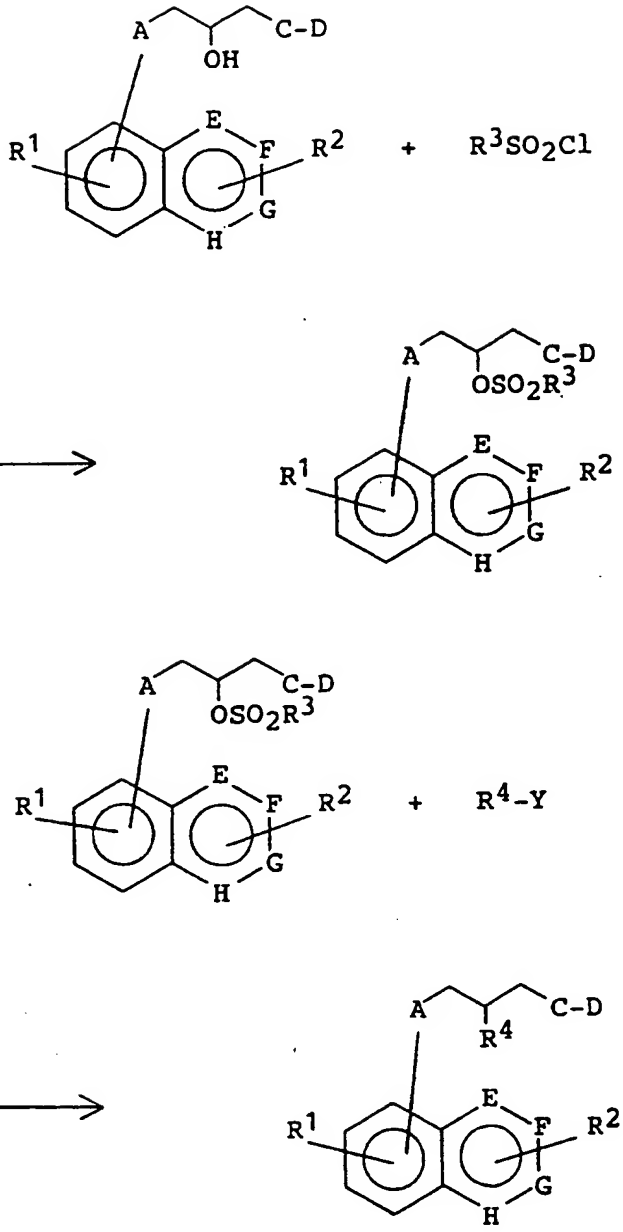


where R^1, R^2, A, C, D, E, F, G, H and X are as defined above.

The above-mentioned "thermally" means in the temperature range of from room temperature to a boiling point of the used solvent. The solvent used is an organic solvent such as acetone, chloroform, an alcohol or DMF.

A fifth method of synthesizing compounds of the present invention is as follows: The hydroxyl group of the compound which has been obtained by the first or second method is reacted with a corresponding acyl chloride or the like, thereby preparing a compound having the general formula (I) wherein B is $-CH_2CH(OCOR^3)CH_2-$. Alternatively, the above compound is reacted with p-toluenesulfonyl chloride or methanesulfonyl chloride, and the resultant product is then reacted with an alkoxide of an alkaline metal or an alkylamine to perform a substitutional reaction, thereby preparing the compound of the general formula (I) wherein B is $-CH_2CH(R^4)CH_2-$.


A
C-D
OH
E
F
R1
R2
G
H
+
R3COCl
A
C-D
OCOR3
E
F
R1
R2
G
H



wherein R^1, R^2, A, C, D, E, F, G and H are as defined above, R^3 is a hydrogen atom or a lower alkyl group, R^4 is a lower alkoxy group, lower acyloxy group or lower alkylamino group, and Y is an alkaline metal or hydrogen atom.

The present invention will now be described in detail wtih reference to the following examples, but the scope of the present invention is not be limited to these examples.

The relative ability of the compounds of the present invention to potentiate the effect of anticancer drugs on drug-resistant cancer was assessed by measuring the incorporation of anticancer drugs into cells and by enforcement of therapeutic activity of anticancer drugs, using an adriamycin-resistant strain 2780AD of human ovarian cancer cells or an adriamycin-resistant strain K562/ADM of human myeloleukemia cells. Adriamycin is an anticancer drug.

The compounds according to the present invention manifest remarkable reinforcement activity in the incorporation of anticancer drugs and reinforcement activity in therapeutic effect of anticancer drugs, which will be explained in detail in the following Examples.

Anticancer drugs suitable for use in combination with the compounds or the salts thereof according to the present invention are not specifically limited: those preferably used are, for example, non-antimetabolites such as anthracycline group antibiotics, e.g. adriamycin, daunomycin or acrasinomycin A, actinomycin group antibiotics, e.g. actinomycin C or actinomycin D, chromomycin group antibiotics, e.g. mithramycin or toyomycin, vincalkaloids, e.g. vincristine or vinblastine, meitansins, podophyllotoxin derivatives, e.g. VP16-213, homoharintonin, angwindin, bruceantin, neocarcinostatin, anthramycin, mitomycin C and cisplatin derivatives.

The compounds and the salts thereof according to the present invention can be administered independently with before or after the administration of anticancer drugs or in combination with anticancer drugs in the same delivered dosage unit. The compounds and their salts according to the present invention can be administered as preparations suited to various means of administration independently with various anticancer drugs or, alternatively, can be administered as preparations mixed with anticancer drugs. Modes of administration are naturally different depending on the symptom(s) of patients to be treated. Physical form of anticancer drugs, etc. Amounts in the range between 1 and 1,000 mg/day for an adult in a single or divided doses can be used orally in forms such as tablets, granules, powders, suspensions, capsules or syrups, or as parenteral drugs such as injections, depositories or isotonic fluids for infusion.

For example, when prepared in a tablet form, examples of absorbents to be used include crystallized cellulose and calcium silicate, and examples of excipients are corn starch, lactose, calcium phosphate and magnesium stearate among others. Furthermore, examples of injections to be used are in a form of suspension in water or aquous suspension with cotton seed oil, corn oil, peanut oil, olive oil, etc. or emulsion, for example, with compatible surfactants such as HCO-60. The anticancer drugs may be used as they are without modification.

The compounds according to the present invention strongly suppress the outflow of anticancer drugs from cancer cells and, moreover, are characterized by their low toxicity and extremely low incidence of side effects such as hypotonia.

The compounds according to the present invention are effective towards cancer cells, especially those less sensitive or resistant to anticancer drugs, and can thus provide new therapeutic opportunities for those patients afflicted with such cancers and tumors.

The present invention is further illustrated by the following examples.

Example 1

5-[3-(4-Diphenylmethylpiperazine-1-yl)-2-hydroxypropoxy]quinoline

(a) In 20 ml of dried DMF was dissolved 1 g of 5-hydroxyquinoline, and 0.28 g of sodium hydride (60% content) was then added thereto, followed by heating with stirring at 50 °C for 30 minutes. Afterward, 1.92 g of epichlorohydrin was further added to the reaction liquid and the latter was then heated with stirring at 90 °C for 3 hours, and the solvent was distilled off under reduced pressure. Water was then added to the residue, and the liquid was extracted with chloroform. The chloroform extract was then decolored and purified with active carbon, then was dried with anhydrous sodium sulfate, and was distilled off. The residue was then purified through a silica gel column chromatograph by the use of an effluent solvent of chloroform:methanol = 100:1, so that 0.88 g of 5-(2,3-epoxypropoxy)quinoline was obtained in an oily state.

(b) In 20 ml of ethanol were dissolved 0.88 g of the above obtained epoxy compound and 1.1 g of N-diphenylmethylpiperazine, and the liquid was then heated under reflux for 3 hours. After reaction, ethanol was distilled off, and the residue was then purified through a silica gel column chromatograph, using chloroform:methanol = 50:1 as an effluent solvent. Afterward, fractions containing the desired compound were combined. The solvent was then distilled off, and a small amount of ether was added to the residue for the purpose of crystallization. Afterward, the crystals were filtered and dried in order to obtain 1.5 g of 5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxypropoxy]quinoline.

m.p.:	161-163 °C
IR νcm^{-1} (KBr):	3400(br), 2790, 1580, 1265, 1092, 788
NMR δppm ($CDCl_3$):	2.3-2.9 (m,10H), 3.55 (br,s,1H), 4.05-4.25 (m,4H), 6.82 (d,d,1H), 7.1-7.8 (m,13H), 8.54 (d,d,1H), 8.84 (d,d,1H)

Example 2

5-[3-(4-(Dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxypropoxy]quinoline

(a) With 80 ml of dioxane was mixed 11.3 g of anhydrous piperazine, and 5.0 g of 5-chlorobenzosuberane was then added thereto. Afterward, the reaction liquid was heated under reflux for 7 hours. After cooling, insoluble substances were removed by filtration, and the solvent was also distilled off. A small amount of petroleum ether was added to the residue for the purpose of crystallization, the crystals were collected by filtration and were then dried, thereby obtaining 5.1 g of N-(dibenzosuberane-5-yl)-piperazine.

m.p.: 110-111.5 °C

IR νcm^{-1} (KBr): 3420, 3250, 2920, 2800, 1630, 1490, 1450, 1330, 1140

(b) In 20 ml of ethanol were dissolved 0.88 g of the epoxy compound obtained in the step (a) of Example 1 and 1.2 g of N-(dibenzosuberane-5-yl)piperazine, and the liquid was then heated under reflux for 3 hours. After reaction, the solvent was distilled off, and the residue was then purified through a silica gel column chromatograph.

A solvent of chloroform:methanol = 50:1 was used as an effluent solvent, so that 5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxypropoxy]quinoline which was the aimed compound was obtained in an amount of 1.4 g.

IR νcm^{-1} (KBr): 2900, 2800, 1620, 1590, 1570, 1450, 1260, 1140, 1100

NMR δppm ($CDCl_3$): 2.1-3.0 (m,12H), 3.1-3.6 (br,s,1H), 3.7-4.4 (m,6H), 6.8 (d,1H), 6.9-7.9 (m,11H), 8.5 (d,1H), 8.8 (d,1H)

Example 3

5-(3-[N-(2-(N-Diphenylmethyl-N-methylamino)ethyl)-N-methylamino]-2-hydroxypropoxy)quinoline

(a) In 100 ml of dioxane were dissolved 25 g of N,N'-dimethylethylenediamine and 6 g of diphenylmethyl chloride, and the liquid was then heated under reflux for 4 hours. The solvent was distilled off, and water was then added to the residue, followed by extracting with chloroform.

The chloroform extract was then dried with anhydrous sodium sulfate, and the solvent was distilled off.

The residue was then purified through a silica gel column chromatograph by the use of a solvent of chloroform:methanol = 25:1, thereby obtaining 4.6 g of N-diphenylmethyl-N,N'-dimethylethylenediamine in an oily state.

IR νcm^{-1}: 2960, 2860, 2800, 1600, 1500, 1460, 1030

NMR δppm ($CDCl_3$): 1.8 (s,1H), 2.1 (s,3H), 2.35 (s,3H), 2.4-2.8 (m,4H), 4.35 (s,1H), 7.1-7.6 (m,10H)

(b) In 20 ml of ethanol were dissolved 1.06 g of the above obtained amine compound and the epoxy compound obtained in Example 1-(a), and the liquid was then heated under reflux for 3 hours. The solvent was then distilled off under reduced pressure, and the residue was purified through a silica gel column chromatograph by the use of an effluent of chloroform:methanol = 100:1, thereby obtaining 1.3 g of 5-(3-[N-(2-(N-diphenylmethyl-N-methylamino)ethyl)-N-methylamino]-2-hydroxypropoxy)quinoline.

IR νcm^{-1}: 2960, 2800, 1620, 1590, 1580, 1490, 1450, 1280

NMR δppm ($CDCl_3$): 2.2 (s,3H), 2.3 (s,3H), 2.4-3.0 (m,3H), 3.9-4.25 (m,4H), 4.3 (s,1H), 6.9 (d,1H), 7.0-7.8 (m,13H), 8.5 (d,1H), 8.85 (d,1H)

Example 4

5-[3-(4-Diphenylmethylhomopiperazine-1-yl)-2-hydroxypropoxy]quinoline

In 20 ml of ethanol were dissolved 0.88 g of the epoxy compound obtained in Example 1-(a) and 1.2 g of N-diphenylmethylhomopiperazine, and the liquid was then heated under reflux for 3 hours. After reaction, the solvent was distilled off, and the residue was then purified through a silica gel column chromatograph. A solvent of chloroform:methanol = 50:1 was used as an effluent solvent, so that 5-[3-(4-diphenylmethyl-homopiperazine-1-yl)-2-hydroxypropoxy]quinolinewhich was intended therein was obtained in an amount of 1.6 g.

IR νcm^{-1} (KBr): 3040, 3000, 2920, 2820, 1610, 1580, 1570, 1460, 1260, 1170

NMR δppm ($CDCl_3$): 1.8 (t,2H), 2.4-3.2 (m,10H), 3.65 (s,1H), 4.15 (s,3H), 4.6 (s,1H), 6.8 (d,1H), 7.0-7.9 (m,13H), 8.5 (d,1H), 8.8 (d,1H)

Example 5

2,4-Dimethyl-5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxypropoxy]quinoline

(a) With 5.0 g of acetylacetone was mixed 2.8 g of 3-amino-2-cyclohexenone, and the liquid was then heated with stirring at 70 • C for 1 hour. The heating was further continued at a temperature of 160 to 170 • C for 9 hours.

Excess acetylacetone and water were distilled off under reduced pressure, and the residue was then purified through a silica gel column chromatograph by the use of an effluent of chloroform:methanol = 50:1, thereby obtaining 1.85 g of 2,4-dimethyl-5,6,7,8-tetrahydro-5-oxoquinoline.

m.p.: 54-57 • C

(b) In 15 ml of diethylene glycol butylether acetate were dissolved 1.6 g of the above synthesized tetrahydroquinoline compound and 0.2 g of 10% Pd-C, and the liquid was then heated with stirring at 200 • C for 6 hours under a nitogen gas stream.

After cooling, the deposited crystals were separated from Pd-C by filtration, and the solvent was distilled off and the solvent-free filtrate was then purified through a silica gel column chromatograph to obtain the desired product. Furthermore, the deposited crystals were dissolved in methanol, then filtered to remove Pd-C therefrom, and evaporated to dryness under reduced pressure, thereby obtaining the desired compound, 2,4-dimethyl-5-hydroxyquinoline.

Total yield: 0.82 g

m.p.: 222-224 • C

NMR δppm (DMSO-d_6): 2.50 (s,3H), 2.82 (s,3H), 6.7-7.1 (m,2H), 7.20-7.50 (m,2H), 10.0 (s,1H)

(c) Following the same procedure as in Example 1-(a), 0.72 g of the above synthesized hydroxyquinoline compound and epichlorohydrin were subjected to reaction and treatment in order to form an epoxy compound. The latter was further reacted and treated with the diphenylpiperazine compound in accordance with the same procedure as in Example 1-(b), thereby obtaining 1.13 g of 2,4-dimethyl-5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxypropoxy]quinoline.

IR νcm^{-1} (KBr): 3400, 2800, 1600, 1450, 1260, 1050

NMR δppm ($CDCl_3$): 2.5-2.85 (m,16H), 3.65 (br,s,1H), 4.0-4.3 (m,4H), 6.75 (d,1H), 7.0 (s,1H), 7.15-7.6 (m,12H)

Example 6

5-[3-(4-(6,11-Dihydrodibenzo[b,e]oxepine-11-yl)piperazine-1-yl)-2-hydroxypropoxy]quinoline

(a) In 90 ml of dried ether was dissolved 4.05 g of 6H-dibenzo[b,e]oxepine-11-one, and the liquid was then added dropwise, while being cooled with ice, to a solution in which $LiAlH_4$ was dispersed in 70 ml of dried ether.

The liquid was heated under reflux for 4.5 hours and was then cooled, and a saturated aqueous Glauber's salt solution was added thereto.

The liquid was filtered to remove insoluble substances therefrom, followed by drying. The solvent was then distilled off, and the residue was purified through a silica gel column chromatograph by the use of an effluent solvent of chloroform:methanol = 100:1 in order to obtain 4.0 g of 11-hydroxy-6,11-dihydrodibenzo[b,e]oxepine.

IR νcm^{-1} (KBr): 3260, 1600, 1570, 1480, 1440, 1280, 1250

NMR δppm ($CDCl_3$): 1.55 (s,1H), 4.75-4.95 (m,1H), 5.3 (s,1H), 5.8-6.3 (m,1H), 6.5-7.6 (m,8H)

(b) In 70 ml of dried methylene chloride was dissolved 3.6 g of the above obtained 11-hydroxydibenz-[b,e]oxepine, and 3.0 g of thionyl chloride was then added dropwise thereto under cooling with ice. After stirring at room temperature for 1 hour, the excessive solvent and thionyl chloride were distilled off under reduced pressure.

Furthermore, the residue was dissolved in 40 ml of methylene chloride, and the liquid was then added to a solution in which 8.8 g of anhydrous piperazine was dissolved in 90 ml of methylene chloride, followed by stirring at room temperature for 1 hour.

Insoluble substances were removed therefrom by filtration, and the filtrate was washed with water and was then dried.

After the solvent was distilled off, the liquid was purified with a silica gel column chromatograph, using an effluent solvent of chloroform:methanol = 20:1, in order to obtain 3.2 g of 11-piperazino-6,11-dihydrodibenzo[b,e]oxepine.

NMR δppm ($CDCl_3$): 2.1 (s,1H), 2.2-3.0 (m,8H), 3.8 (s,1H), 4.6 (d,1H), 6.7 (s,1H), 6.8-7.3 (m,8H)

(c) Following the same procedure as in Example 1-(b), 2.5 g of the above synthsized dizenzooxepine compound and 1.1 g of the epoxy compound synthesized in Example 1-(a) were subjected to reaction and treatment, thereby obtaining 2.6 g of 5-[3-(4-(6,11-dihydrodibenzo[b,e]oxepine-11-yl)piperazine-1-yl)-2-hydroxypropoxy]quinoline.

IR νcm^{-1} (KBr): 3400, 2930, 2800, 1615, 1590, 1570, 1480, 1450, 1270

NMR δppm ($CDCl_3$): 2.1-3.0 (m,10H), 3.9 (s,1H), 4.05-4.3 (m,3H), 4.7 (d,1H), 6.8 (t,4H), 7.0-7.4 (m,8H), 7.55 (t,1H), 7.7 (d,1H), 8.55 (d,1H), 8.55 (d,1H)

Example 7

5-[3-(4-(Diphenyl-hydroxymethyl)piperidine-1-yl)-2-hydroxypropoxy]quinoline

Reaction and treatment were carried out using 0.4 g of the epoxy compound synthesized in Example 1-(a) and 0.6 g of 4-(diphenyl-hydroxymethyl)piperidine in accordance with the same procedure as in Example 1-(b), in order to obtain 0.75 g of 5-[3-(4-(diphenyl-hydroxymethyl)piperidine-1-yl)-2-hydroxypropoxy]quinoline.

IR νcm^{-1} (KBr): 3380, 2925, 1610, 1580, 1568, 1265 1095, 790, 740, 695

NMR δppm ($CDCl_3$): 1.55 (m,4H), 2.09 (m,1H), 2.3-2.5 (m,2H), 2.5-2.7 (m,2H), 2.95 (m,1H), 3.09 (m,1H), 3.6 (br,2H), 4.0-4.25 (m,3H), 6.80 (d.1H), 7.15 (m,2H), 7.2-7.35 (m,5H), 7.4-7.6 (m,5H), 7.66 (d.1H), 8.53 (dd,1H), 8.81 (dd,1H)

Example 8

5-[3-(4-(2,2-Diphenylacetyl)piperazine-1-yl)-2-hydroxypropoxy]-2-methoxyquinoline

(a) Reaction and treatment were carried out using 1.6 g of 5-hydroxy-2-methoxyquinoline in accordance with the same procedure as in Example 1-(a), in order to obtain 5-(2,3-epoxypropoxy)-2-methoxyquinoline.

NMR δppm ($CDCl_3$): 2.82 (dd,1H), 2.95 (t,1H), 3.4-3.5 (m,1H), 4.0-4.2 (m,1H), 4.06 (s,3H), 4.38 (dd,1H), 6.71 (dd,1H), 6.86 (d,1H), 7.4-7.55 (m,2H), 8.42 (d,1H)

(b) Reaction and treatment were carried out using 0.7 g of the above synthesized epoxy compound and 1.0 g of N-(2,2-diphenylacetyl)piperazine in accordance with the same procedure as in Example 1-(b), in order to obtain 1.39 g of 5-[3-(4-(2,2-diphenylacetyl)piperazine-1-yl)-2-hydroxypropoxy]-2-methoxyquinoline.

IR νcm^{-1} (KBr): 1630, 1610, 1590, 1570, 1430, 1395, 1310, 1240

NMR δppm ($CDCl_3$): 2.2-2.8 (m,6H), 3.4-3.6 (m,2H), 3.6-3.9 (m,2H), 3.9-4.3 (m,6H), 5.19 (s,1H), 6.6-6.75 (m,1H), 6.85 (d,1H), 7.0-7.6 (m,14H), 8.34 (d,1H)

Example 9

5-[3-(4-(Dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxypropoxy]-2-methoxyquinoline

Reaction and treatment were carried out using 0.7 g of the epoxy compound synthesized in Example 8-(a) and 0.92 g of the dibenzosuberanylpiperazine compound synthesized in Example 2-(a), in order to obtain 1.22 g of the desired compound.

IR νcm^{-1} (KBr): 3040, 3000, 2920, 2800, 1610, 1595, 1570, 1430, 1395, 1310, 1200

NMR δppm ($CDCl_3$): 2.2-2.9 (m,12H), 3.9-4.2 (m,6H), 4.05 (s,3H), 6.71 (dd,1H), 6.84 (d,1H), 7.0-7.3 (m,8H), 7.4-7.52 (m,2H), 8.37 (d,1H)

Example 10

5-(3-[N-(2-(N-Diphenylmethyl-N-ethylamino)ethyl)-N-ethylamino]-2-hydroxypropoxy)quinoline

(a) Reaction and treatment were carried out using 21 g of N,N'-diethylethylenediamine and 7.3 g of diphenylmethyl chloride in accordance with the same procedure as in Example 3-(a), in order to obtain 4.2 g of N-diphenylmethyl-N,N'-diethylethylenediamine.

NMR δppm ($CDCl_3$): 0.9-1.4 (m,6H), 2.4-3.2 (m,8H), 4.8 (s,1H), 7.1-7.8 (m,10H)

(b) Reaction and treatment were carried out using 1.52 g of the above synthesized diamine compound and 1.08 g of the epoxy compound synthesized in Example 1-(a) in accordance with the same procedure as in Example 1-(b), in order to obtain 0.5 g of 5-(3-[N-(2-(N-diphenylmethyl-N-ethylamino)ethyl)-N-ethylamino]-2-hydroxypropoxy)quinoline.

IR νcm^{-1} (KBr): 3400, 1630, 1590, 1450, 1410, 1280, 1100

NMR δppm ($CDCl_3$): 1.0 (m,6H), 2.3-2.9 (m,10H), 3.95-4.2 (m,4H), 6.85 (d,1H), 7.0-7.85 (m,11H), 8.55 (d,1H), 8.9 (d,1H)

Example 11

5-[3-(4-(2,3,3',4'-Tetramethoxydiphenylmethyl)piperazine-1-yl)-2-hydroxypropoxy]quinoline

(a) Following the same procedure as in Example 6-(b), reaction and treatment were carried out using 3.45 g of 2,3,3',4'-tetramethoxybenzohydrol in order to obtain 3.1 g of N-(2,3,3',4'-tetramethoxydiphenylmethyl)piperazine.

NMR δppm ($CDCl_3$): 1.9 (s,1H), 2.35 (s,4H), 2.85 (t,4H), 3.8 (s,12H), 4.7 (s,1H), 6.75 (m,2H), 7.0 (m,3H), 7.25 (s,1H)

(b) Following the same procedure as in Example 1-(b), reaction and treatment were carrried out using 3.1 g of the above synthesized piperazine derivative and 0.86 g of the epoxy compound synthesized in Example 1-(a), in order to obtain 1.82 g of 5-[3-(4-(2,3,3',4'-tetramethoxydiphenylmethyl)piperazine-1-yl)-2-hydroxypropoxy]quinoline.

IR νcm^{-1} (KBr): 3400, 2920, 1640, 1595, 1520, 1480, 1420, 1280

NMR δppm ($CDCl_3$): 1.8-2.3 (m, 1H), 2.3-2.9 (m,10H), 3.5-4.0 (s,12H), 4.05-4.4 (m,3H), 4.7 (s,1H), 6.75 (q,2H), 6.85 (d,1H), 6.95-7.1 (m,3H), 7.25 (s,1H), 7.35 (q.1H), 7.55 (t,1H), 7.7 (d,1H), 8.55 (d,1H), 8.9 (q,1H)

Example 12

3-Ethyl-5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxypropoxy]quinoline

In 10 ml of DMF was dissolved 750 mg of 3-ethyl-5-hydroxyquinoline, and 180 mg of 60% sodium hydride was then added thereto. The solution was stirred at 50°C for 30 minutes, and 1.25 g of epichlorohydrin was then added thereto, followed by stirring at 90°C for 3 hours. Afterward, the solvent was distilled off, and the residue was dissolved in chloroform and was then washed with water. The chloroform layer was dried and concentrated, and this residue was dissolved in 10 ml of ethanol. Furthermore, 750 mg of N-diphenylmethylpiperazine

was added thereto, and the liquid was then heated under reflux for 3 hours.

The solvent was then distilled off, and the residue was purified through a silica gel column chromatograph by the use of an effluent solvent of chloroform:methanol = 50:1, thereby obtaining 800 mg of 3-ethyl-5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxypropoxy]quinoline.

IR νcm^{-1} (KBr): 3450, 2805, 1600, 1578, 1450, 1262, 1090, 742, 705

NMR δppm ($CDCl_3$): 1.32 (t,3H), 2.3-2.85 (m,12H), 4.0-4.25 (m,4H), 6.80 (d,1H), 7.1-7.28 (m,6H), 7.37-7.5 (m,5H), 7.64 (d,1H), 8.28 (d,1H), 8.73 (d,1H)

Example 13

5-[3-(4-(Diphenylmethylene)piperidine-1-yl)-2-hydroxypropoxy]quinoline

Following the same procedure as in Example 1-(b), reaction and treatment were carried out using 1.25 g of 4-(diphenylmethylene)piperidine, thereby obtaining 0.96 g of the desired compound.

NMR δppm ($CDCl_3$): 2.3-3.0 (m,10H), 4.1-4.4 (m,3H), 6.87 (d,1H), 7.0-7.5 (m,11H), 7.5-7.8 (m,2H), 8.5-8.75 (m,1H), 8.75-9.0 (m,1H)

Example 14

5-[3-(4-(Diphenylmethyl)piperidine-1-yl)-2-hydroxypropoxy]quinoline

Following the same procedure as in Example 1-(b), reaction and treatment were carried out using 1.09 g of 4-(diphenylmethyl)piperidine, thereby obtaining 0.14 g of the desired compound.

NMR δppm ($CDCl_3$ + DMSO-d_6): 1.6-1.9 (m,4H), 2.3-2.5 (m,1H), 2.5-2.7 (m,3H), 2.7-3.0 (m,1H), 3.0-3.3 (m,1H), 3.3-3.7 (m,3H), 4.1-4.3 (m,2H), 4.55-4.75 (m,1H), 6.83-6.94 (m,1H), 7.68-7.70 (m,13H), 8.6-8.7 (m,1H), 8.84-8.92 (m,1H)

Example 15

5-[2-Hydroxy-3-(4-(phenyl-2-pyridylmethyl)piperazine-1-yl)propoxy]quinoline

Following the same procedure as in Example 1-(b), reaction and treatment were carried out using 0.93 g of N-(phenyl-2-pyridylmethyl)piperazine to obtain 1.22 g of the desired compound.

NMR δppm ($CDCl_3$): 1.57 (s,1H), 2.3-2.9 (m,10H), 4.05-4.30 (m,3H), 4.45 (s,1H), 6.87 (d,1H), 7.05-7.72 (m,12H), 8.52 (d,1H), 8.58 (d,1H), 8.90 (dd,1H)

Example 16

5-[3-(4-(2,2-Diphenylacetyl)piperazine-1-yl)-2-hydroxypropoxy]quinoline

Following the same procedure as in Example 1-(b), reaction and treatment were carried out using 0.85 g of the epoxy compound synthesized in Example 1-(a) and 1.12 g of N-(2,2-diphenylacetyl)piperazine to obtain 1.2 g of the desired compound.

NMR δppm ($CDCl_3$): 2.1-2.3 (m,1H), 2.3-2.75 (m,5H), 3.3-3.6 (m,3H), 3.6-3.8 (m,2H), 4.05-4.25 (m,3H), 5.18 (s,1H), 6.83 (d,1H), 7.1-7.45 (m,11H), 7.57 (t,1H), 7.69 (d,1H), 8.4-8.55 (m,1H)

Example 17

5-[3-(4-(2,2-Diphenylethyl)piperazine-1-yl)-2-hydroxypropoxy]quinoline

Following the same procedure as in Example 1-(b), reaction and treatment were carried out using 0.85 g of the epoxy compound synthesized in Example 1-(a) and 1.07 g of N-(2,2-diphenylethyl)piperazine to obtain 1.2 g of the desired compound.

NMR δppm ($CDCl_3$): 2.3-2.75 (m,10H), 2.97 (d,2H), 4.0-4.25 (m,4H), 6.85 (d,1H), 7.10-7.70 (m,13H), 8.45-8.55 (m,1H), 8.80-8.92 (m,1H)

Example 18

5-[3-(4-(5-Dibenzosuberanyl)piperazine-1-yl)-2-hydroxypropoxy]-2-chloroquinoline

(a) Following the same procedure as in Example 1-(a), reaction and treatment were carried out using 0.8 g of 2-chloro-5-hydroxyquinoline to obtain 0.62 g of 2-chloro-5-(2,3-epoxypropoxy)quinoline.

IR νcm^{-1} (KBr): 3040, 2980, 2820, 1610, 1580, 1490, 1460, 1395, 1370, 1290, 1260, 1200, 1170, 1140, 1130, 1075, 1060, 900, 860, 820, 790, 740

(b) Following the same procedure as in Example 1-(b), reaction and treatment were carried out using 0.32 g of the above sinthesized epoxy compound and 0.37 g of N-(dibenzosuberanyl)piperazine synthesized in Example 2-(a), in order to obtain 0.63 g of 5-[3-(4-(dibenzosuberanyl)piperazine-1-yl)-2-hydroxypropoxy]-2-chloroquinoline.

NMR δppm ($CDCl_3$): 2.15-2.9 (m,12H), 3.9-4.25 (m,6H), 6.75-6.95 (m,1H), 6.95-7.40 (m,9H), 7.58 (d,1H9, 8.47 (d,1H)

Example 19

5-[3-(4-(Diphenyl-hydroxymethyl)piperidine-1-yl)-2-hydroxypropoxy]-2-chloroquinoline

Following the same procedure as in Example 1-(b), reaction and treatment were carried out using 0.31 g of the epoxy compound synthesized in Example 18-(a) and 0.35 g of 4-(diphenyl-hydroxymethyl)-piperidine to obtain 0.52 g of the desired compound.

NMR δppm ($CDCl_3$): 1.35-1.6 (m,4H), 1.95-2.7 (m,6H), 2.8-3.0 (m,1H), 3.0-3.2 (m,1H), 4.0-4.25 (m,3H), 6.8-6.9 (m,1H), 7.1-7.65 (m,13H), 8.48 (d,1H)

Example 20

5-[3-(4-(5-Dibenzosuberenyl)piperazine-1-yl)-2-hydroxypropoxy]quinoline

Following the same procedure as in Example 1-(b), reaction and treatment were carried out using 0.4 g of the epoxy compound synthesized in Example 1-(a) and 0.6 g of N-(dibenzosuberenyl)piperazine to obtain 0.85 g of the desired compound.

NMR δppm ($CDCl_3$): 1.9-2.7 (m,10H), 4.0-4.25 (m,3H), 4.29 (s,1H), 6.82 (d,1H), 6.96 (s,2H), 7.15-7.80 (m,11H), 8.40-8.50 (m,1H), 8.80-8.90 (m,1H)

Example 21

2,4-Dimethyl-5-[3-(4-(6,11-dihydrodibenzo[b,e]oxepine-11-yl)piperazine-1-yl)-2-hydroxypropoxy]quinoline

Following the same procedure as in Example 5-(c), reaction and treatment were carried out using 0.8 g of 2,4-dimethyl-5-hydroxyqunoline prepared in Example 5-(b) and 1.04 g of 11-piperazino-6,11-dihydro-dibenzo[b,e]oxepine prepared in Example 6-(b), in order to obtain 1.6 g of the desired compound.

IR νcm^{-1} (KBr): 3400, 1630, 1594, 1440, 1380, 1260

NMR δppm ($CDCl_3$): 2.25-2.6 (m,10H), 2.6 (s,3H), 2.85 (s,3H), 3.9 (s,1H), 4.05-4.25 (m,3H), 4.7 (d,1H), 6.8 (m,4H), 6.95 (s,1H), 7.05-7.35 (m,6H), 7.5 (t,1H), 7.6 (d,1H)

Example 22

5-[3-(4-(Dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxypropoxy]-2,4-dimethylquinoline

Following the same procedure as in Example 5-(c), reaction and treatment were carried out using 0.8 g of 2,4-dimethyl-5-hyroxyquilne synthesized in Example 5-(b) and 1.04 g of dibenzosuberanylpiperazine synthesized in Example 2-(a), in order to obtain 1.6 g of the desired compound.

NMR δppm ($CDCl_3$): 2.2-2.9 (m,12H), 2.62 (s,3H), 2.83 (s,3H), 3.9-4.25 (m,6H), 6.75 (d,1H), 6.95-7.25 (m,9H), 7.48 (t,1H), 7.59 (d,1H)

Example 23

5-[3-(4-Diphenylmethylpiperazine-1-yl)-2-hydroxypropoxy]-6-methylquinoline

(a) In 20 ml of a 80% aqueous sulfuric acid solution were dissolved 3.48 g of 3-amino-6-methylphenol, 5.5 ml of glycerol and 7 g of sodium m-nitrobenzene sulfonate, and the liquid was then heated with stirring at 150 °C for 1 hour.

After cooling, the liquid was neutralized with an aqueous sodium hydroxide solution to a pH of 8 to 9. The resulting aqueous layer was removed therefrom by filtration, and the residue was then dissolved in methanol and insoluble substances were afterward filtered off.

The methanol solution was concentrated and then purified through a silica gel column chromatograph by the use of an effluent solvent of chloroform:methanol = 25:1, thereby obtaining 0.17 g of 5-hydroxy-6-methylquinoline and 1.6 g of 7-hydroxy-6-methylquinoline.

5-Hydroxy-6-methylquinoline:

IR νcm^{-1} (KBr): 1578, 1255, 1178, 1082, 915, 800
NMR δppm (CMSO-d_6): 2.4 (s,3H), 7.42 (dd,1H), 7.5 (s,1H), 8.62 (dd,1H), 8.78 (dd,1H), 9.3 (br,1H)

7-Hydroxy-6-methylquinoline:

NMR δppm (CMSO-d_6): 2.38 (s,3H), 7.31 (dd,1H), 7.4 (s,1H), 7.7 (s,1H), 8.20 (dd,1H), 8.72 (dd,1H)

(b) In 50 ml of acetone were dissolved 5.04 g of diphenylmethylpiperazine and 5.5 g of epichlorohydrin, and 4.2 ml of triethylamine was then added thereto.

The liquid was heated under reflux for 2 hours, and the solvent was then distilled off under reduced pressure. The residue was purified by a silica gel column chromatograph to obtain 2.9 g of 4-(3-chloro-2-hydroxypropyl)-1-diphenylmethylpiperazine and 2.8 g of 4-(2,3-epoxypropyl)-1-diphenylmethylpiperazine.

4-(3-Chloro-2-hydroxypropyl)-1-diphenylmethylpiperazine:

NMR δppm ($CDCl_3$): 2.2-2.9 (m,10H), 3.5-4.0 (m,3H), 4.20 (s,1H), 7.0-7.5 (m,10H)

4-(2,3-Epoxypropyl)-1-diphenylmethylpiperazine:

NMR δppm ($CDCl_3$): 2.1-2.8 (m,12H), 2.9-3.1 (m,1H), 4.20 (s,1H), 7.0-7.5 (m,10H)

(c) In 10 ml of dried THF were dissolved 170 mg of 5-hydroxy-6-methylquinoline synthesized in the preceding step (a) and 395 mg of 4-(3-chloro-2-hydroxypropyl)-1-diphenylmethylpiperazine synthesized in the preceding step (b), and 143 mg of t-BuOK was then added thereto.

Afterward, the liquid was heated under reflux for 10 hours and was then poured into an aqueous ammonium chloride solution, and it was then extracted with chloroform. The extract was dried with anhydrous magnesium sulfate and then concentrated.

The residue was purified through a silica gel column chromatograph by the use of an effluent solvent of chloroform:methanol = 50:1, thereby obtaining 100 mg of 5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxypropoxy]-6-methylquinoline.

NMR δppm ($CDCl_3$): 3.46 (s,3H), 2.2-3.0 (m,10H), 3.7 (br,s,1H), 3.8-4.1 (m,2H), 4.0-4.2 (m,1H), 4.23 (s,1H), 7.7-7.0 (m,12H), 7.88 (d,1H), 8.60 (dd,1H), 8.86 (dd,1H)

Example 24

5-[3-(4-Diphenylmethylpiperazine-1-yl)-2-hydroxypropoxy]-8-methylquinoline

(a) Following the same procedure as in Example 23-(a), reaction and treatment were carried out using 3.9 g of 3-amino-4-methylphenol, 7 ml of glycerol, 8.7 g of sodium m-nitrobezene sulfonate and 29 ml of a 80% aqueous sulfuric acid solution in order to obtain 290 mg of 5-hydroxy-8-methylquinoline.

NMR δppm (DMSO-d_6): 6.8 (d,1H), 7.3 (d,1H), 7.3 (dd,1H), 8.5 (dd,1H), 7.8 (dd,1H), 10.0 (br,s,1H)

(b) Following the same procedure as in Example 23-(c), reaction and treatment were carried out using 360 mg of the above synthesized 5-hydroxy-8-methylquinoline, 1.39 g of 4-(3-chloro-2-hydroxypropyl)-1-diphenylmethylpiperazine and 300 mg of t-BuOK in order to obtain 120 mg of 5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxypropoxy]-8-methylquinoline.

IR νcm^{-1} (KBr): 3350, 2900, 1610, 1580, 1540, 1430, 1360, 1270, 1230, 1200, 1080, 900, 800, 740, 690
NMR δppm ($CDCl_3$): 2.4-2.7 (m,10H), 3.79 (br,s,1H), 4.0-4.2 (m,3H), 4.2 (s,1H), 6.7 (d,1H), 7.1-7.4 (m,12H), 8.5 (dd,1H), 8.9 (dd.1H)

Example 25

5-[3-(4-Diphenylmethylpiperazine-1-yl)-2-hydroxypropoxy]-8-methoxyquinoline

(a) Following the same procedure as in Example 23-(a), reaction and treatment were carried out using 2.25 g of 3-amino-4-methoxyphenol, 3.7 ml of glycerol and sodium m-nitrobenzene sulfonate to obtain 180 mg of 5-hydroxy-8-methoxyquinoline.

NMR δppm ($CDCl_3$ + DMSO-d_6): 4.0 (s,3H), 6.90 (s,2H), 7.41 (dd,1H), 8.58 (dd,1H), 8.90 (dd,1H),

9.30 (br,1H)

(b) Following the same procedure as in Example 23-(c), reaction and treatment were carried out using 180 mg of 5-hydroxy-8-methoxyquinoline to obtain 140 mg of 5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxy-propoxy]-8-methoxyquinoline.

IR νcm^{-1} (KBr): 3360, 2500, 1620, 1580, 1540, 1470, 1440, 1400, 1370, 1280, 1100, 900, 800, 730

NMR δppm ($CDCl_3$): 2.5-2.8 (m,10H), 3.28 (br,s,1H), 4.03 (s,3H), 4.0-4.2 (m,2H), 4.24 (s,1H), 6.77 (d,1H), 6.90 (d,1H), 7.15-7.45 (m,11H), 8.54 (dd,1H), 8.93 (dd,1H)

Example 26

5-[3-(4-Diphenylmethylpiperazine-1-yl)-2-hydroxypropoxy]-8-nitroquinoline

Following the same procedure as in Example 23-(c), reaction and treatment were carried out using 180 mg of 5-hydroxy-8-nitroquinoline to obtain 15 mg of the desired compound.

IR νcm^{-1} (KBr): 3350, 2900, 2400, 1610, 1570, 1510, 1420, 1310, 1270, 1180, 1080, 1000, 900, 730

NMR δppm ($CDCl_3$): 2.5-2.9 (m,10H), 4.2-4.3 (m,4H), 6.7 (d,1H), 7.1-7.4 (m,11H), 8.2 (d,1H), 8.7 (dd,1H), 9.1 (dd,1H)

Example 27

5-[3-(4-Diphenylmethylpiperazine-1-yl)-2-hydroxypropylamino]quinoline

In 20 ml of chloroform were dissolved 1.11 g of 5-aminoquinoline and 1.19 g of 4-(3-chloro-2-hydroxypropyl)-1-diphenylmethylpiperazine, and the liquid was then heated at a temperature of 180 to 200 °C for 4 hours in an autoclave.

The reaction liquid was then concentrated, and the residue was purified through a silica gel column chromatograph by the use of ethyl acetate as an effluent solvent, thereby obtaining 460 mg of 5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxy-propylamino]quinoline.

IR νcm^{-1} (KBr): 3220, 2500, 1620, 1570, 1510, 1410, 1330, 1290, 1010

NMR δppm ($CDCl_3$): 2.2-2.8 (m,10H), 3.1-3.5 (m,2H), 3.6 (br,1H), 4.0-4.2 (m,1H), 4.21 (s,1H), 5.1 (br,1H), 6.57 (d,1H), 7.1-7.5 (m,12H), 8.25 (d,1H), 8.84 (d,1H)

Example 28

5-[3-(4-Diphenylmethylpiperazine-1-yl)-2-hydroxypropylamino]-8-methoxyquinoline

Following the same procedure as in Example 27, reaction and treatment were carried out using 1.81 g of 5-amino-8-methoxyquinoline and 1.23 g of 4-(3-chloro-2-hydroxypropyl)-1-diphenylmethylpiperazine to obtain 200 mg of 5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxy-propylamino]-8-methoxyquinoline.

IR νcm^{-1} (KBr): 3350, 2900, 2780, 1600, 1580, 1470, 1440, 1390, 1270, 1090, 990, 730, 690

NMR δppm ($CDCl_3$): 2.4-2.7 (m,10H), 3.09 (dd,1H), 3.30 (dd,1H), 4.0 (s,3H), 40-4.2 (m,1H), 4.22 (s,1H), 4.5 (br,1H), 6.54 (d,1H), 6.92 (d,1H), 7.1-7.4 (m,11H), 8.25 (dd,1H), 8.90 (dd,1H)

Example 29

5-[3-(4-Diphenylmethylpiperazine-1-yl)-2-hydroxypropoxy]-8-chloroquinoline

Following the same procedure as in Example 23-(c), reaction and treatment were carried out using 0.64 g of 8-chloro-5-hydroxyquinoline and 1.48 g of 4-chloro-2-hydroxypropyl)-1-diphenylmethylpiperazine synthesized in Example 23-(b), in order to obtain 0.68 g of 5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxypropoxy]-8-chloroquinoline.

IR νcm^{-1} (KBr): 3400, 2920, 2800, 1600, 1580, 1300, 1250, 1150, 1080, 1000

NMR δppm ($CDCl_3$): 2.1-3.3 (m,10H), 4.0-4.2 (m,4H), 4.22 (s,1H), 6.70 (d,1H), 7.07-7.45 (m,11H), 7.67 (d,1H), 8.58 (dd,1H), 9.02 (dd,1H)

Example 30

N-[3-(4-Diphenylmethylpiperazine-1-yl)-2-hydroxypropyl]-N-methyl-5-quinolineamine

(a) With 7.2 g of 5-aminoquinoline was mixed 40 ml of ethyl orthoformate, and the liquid was then heated under reflux for 5 hours. An excessive amount of ethyl orthoformate was distilled off, and the residue was then dissolved in 250 ml of anhydrous ethanol. Afterward, 3.8 g of sodium boron hydride was added thereto under cooling with ice. The liquid was allowed to stand at room temperature overnight, and it was then heated at a temperature of 40 to 50 °C for 2 hours.

Afterward, the solvent was distilled off under reduced pressure, and water was then added to the liquid. The latter was extracted with methylene chloride, and the extract was then dried with anhydrous Glauber's salt. The solvent was distilled off, and the residue was then washed with ether to obtain 3.3 g of 5-(methylamino)quinoline.

NMR δppm ($CDCl_3$): 3.05 (d,3H), 4.4 (dr,1H), 6.6 (dd,1H), 7.1-7.7 (m,3H), 8.2 (dd,1H), 8.8 (dd,1H)

(b) In 15 ml of THF was dissolved 0.59 g of the above synthesized 5-(methylamino)quinoline, and 2.36 ml of a 1.6 M n-BuLi hexane solution was added thereto under cooling with ice. Next, a solution was added thereto which had been prepared by dissolving 1.42 g of 4-(3-chloro-2-hydroxypropyl)-1-diphenylmethylpiperazine in 8 ml of THF. Furthermore, 2.36 ml of a 1.6 M n-BuLi hexane solution was added thereto, and the liquid was then allowed to stand at room temperature overnight. The reaction liquid was added to an aqueous ammonium chloride solution and was then extracted with methylene chloride.

The extract was dried with anhydrous magnesium sulfate and was then concentrated, and the residue was purified through a silica gel column chromatograph by the use of an effluent solvent of methylene chloride:methanol = 20:1, thereby obtaining 230 mg of N-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxypropyl]-N-methyl-5-quinolineamine.

IR νcm^{-1} (KBr): 3400, 2600, 1630, 1590, 1450, 1410

NMR δppm ($CDCl_3$): 2.1-2.6 (m,6H), 2.90 (s,3H), 3.00 (dd,1H), 3.19 (dd,1H), 3.59 (br,s,1H), 3.95-4.03 (m,1H), 4.20 (s,1H), 7.0-7.5 (m,12H), 7.58 (dd,1H), 7.85 (d,1H), 8.69 (d,1H), 8.86 (d,1H)

Example 31

5-[3-(4-Diphenylmethylpiperazine-1-yl)-2-hydroxypropylthio]quinoline

Following the same procedure as in Example 23-(c), reaction and treatment were carried out using 220 mg of 5-quinolinethiol and 1.2 g of 4-(3-chloro-2-hydroxypropyl)-1-(diphenylmethyl)piperazine, in order to obtain 130 mg of 5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxypropylthio]quinoline.

NMR δppm ($CDCl_3$): 2.2-2.7 (m,10H), 3.0-3.1 (m,2H), 3.9 (m,1H), 4.20 (s,1H), 7.1-7.8 (m,13H), 8.00 - (d,1H), 8.75 (d,1H), 8.93 (d,1H)

Example 32

5-[3-(4-Diphenylmethylpiperazine-1-yl)propoxy]quinoline

(a) Following the same procedure as in Example 1-(a), reaction and treatment were carried out using 1.0 g of 5-hyroxyquinoline, 2.1 g of 1,3-dibromopropane and 0.78 g of t-BuOK as a base, in order to obtain 0.65 g of 5-(3-bromopropoxy)quinoline.

(b) Following the same procedure as in Example 1-(b), reaction and treatment were carried out using 0.65 g of the above synthesized bromo-compound and 0.62 g of N-diphenylmethylpiperazine, in order to obtain 0.65 g of 5-[3-(4-diphenylmethylpiperazine-1-yl)propoxy]quinoline.

IR νcm^{-1} (KBr): 3400, 1600, 1450, 1420, 1380, 1280, 1100

NMR δppm ($CDCl_3$): 2.0-2.15 (t,2H), 2.3-2.7 (m,10H), 4.15 (t,2H), 4.23 (s,1H), 6.81 (d,1H), 7.16-7.7 (m,13H), 8.55 (d,1H), 8.88 (d,1H)

Example 33

5-[4-(4-Diphenylmethylpiperazine-1-yl)butoxy]quinoline

Following the same procedure as in Example 32-(a), reaction and treatment were carried out using 1.0 g of 5-hydroxyquinoline and 2.3 g of 1,4-dibromobutane to obtain 0.78 g of 5-(4-bromobutoxy)quinoline. Furthermore, the same procedure as in Example 32-(b) was repeated with the exception that 0.78 g of N-diphenylmethylpiperazine was used, in order to perform reaction and treatment, so that 0.8 g of the desired compound was obtained.

IR νcm^{-1} (KBr): 3420, 1635, 1595, 1415, 1280

NMR δppm ($CDCl_3$): 1.7-2.1 (m,4H), 2.3-2.8 (m,10H), 4.1-4.3 (m,3H), 6.8 (d,1H), 7.1-7.8 (m,13H), 8.55 (d,1H), 8.9 (d,1H)

Example 34

5-[2-(4-Diphenylmethylpiperazine-1-yl)ethoxy]quinoline

Following the same procedure as in Example 32-(a), reaction and treatment were carried out using 1.05 g of 5-hydroxyquinoline and 2.04 g of 1,2-dibromoethane to obtain 0.2 g of 5-(2-bromoethoxy)quinoline.

Furthermore, the same procedure as in Example 32-(b) was repeated with the exception that 0.2 g of N-diphenylmethylpiperazine was used, to perform reaction and treatment, so that 0.1 g of the desired compound was obtained.

NMR δppm ($CDCl_3$): 2.4-3.2 (m,10H), 4.2-4.5 (m,3H), 6.85 (d,1H), 7.1-7.8 (m,13H), 8.5 (d,1H), 8.9 (d,1H)

Example 35

5-[3-(4-Diphenylmethypiperazine-1-yl)propionamido]quinoline

(a) In 60 ml of methylene chloride was dissolved 4.5 g of 5-aminoquinoline, and 10.5 g of 3-chloropropionyl chloride and 9 g of triethylamine were then added thereto. After the liquid was allowed to stand at room temperature overnight, a 1 N aqueous sodium hydroxide solution was added to the liquid, and the latter was then extracted with methylene chloride. The extract was washed twice with an aqueous sodium bicarbonate solution, was then dried, and was concentrated to obtain crystals. The latter were washed with methylene chloride, and filtered to obtain 2.2 g of 5-(3-chloropropionamido)quinoline in a crystalline state.

NMR δppm ($CDCl_3$): 2.9 (t,2H), 3.3 (s,1H), 3.9 (t,2H), 7.0-8.5 (m,5H), 8.9 (dd,1H)

(b) Following the same procedure as in Example 1-(b), 1.1 g of the above synthesized chloro-compound and 1.2 g of N-diphenylmethylpiperazine synthesized in Example 1-(b) were reacted and treated in an ethanol solvent to obtain 1.0 g of 5-[3-(4-diphenylmethylpiperazine-1-yl)propionamide)]quinoline.

IR νcm^{-1} (KBr): 3420, 2580, 1690, 1630, 1600, 1550, 1420, 1370, 1280

NMR δppm ($CDCl_3$): 2.4-3.9 (m,12H), 4.29 (s,1H), 7.1-7.5 (m,11H), 7.69 (t,1H), 7.88 (d,1H), 8.21 (d,1H), 8.35 (d,1H), 8.92 (d,1H), 11.09 (s,1H)

Example 36

5-[3-(4-Dibenzosuberane-5-yl)piperazine-1-yl)propionamido]quinoline

Following the same procedure as in Example 1-(b), 1.1 g of the chloro-compound synthesized in Example 35-(a) and 1.32 g of N-(dibenzosuberane-5-yl)piperazine synthesized in Example 2-(a) were reacted and treated in an ethanol solvent to obtain 1.6 g of 5-[3-(4-dibenzosuberanylpiperazine-1-yl)propionamido]quinoline.

IR νcm^{-1} (KBr): 3400, 2620, 1690, 1630, 1590, 1530, 1410, 1280

NMR δppm ($CDCl_3$): 2.2-3.0 (m,14H), 3.9-4.1 (m,3H), 7.0-7.2 (m,8H), 7.50 (dd,1H), 7.73 (t,1H), 7.92 (d,1H), 8.20 (d,1H), 8.46 (d,1H), 9.01 (d,1H), 11.1 (s,1H)

Example 37

5-[N-Methyl-(3-(4-diphenylmethylpiperazine-1-yl)propionamido)]quinoline

In 30 ml of methylene chloride was dissolved 474 mg of 5-(methylamino)quinoline synthesized in Example 30-(a), and 850 mg of 3-chloropropionyl chloride and 0.5 ml of triethylamine were added thereto at room temperature. After standing at room temperature overnight, a 1 N aqueous sodium hydroxide solution was then added to the liquid so as to alkalinize it. The alkaline liquid was extracted with methylene chloride, and the extract was then washed twice with an aqueous sodium bicarbonate solution and dried with anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and 756 mg of N-(diphenylmethyl)piperazine was added to the residue. The liquid was reacted and treated in an ethanol solvent in accordance with the same procedure as in Example 1-(b) to obtain 880 mg of 5-[N-methyl-(3-(4-diphenylmethylpiperazine-1-yl)propionamido)]quinoline.

IR νcm^{-1} (KBr): 3400, 2520, 1650, 1500, 1410, 1120

NMR δppm ($CDCl_3$): 1.9-2.50 (m,10H), 2.64 (br,t,2H), 3.34 (s,3H), 4.13 (s,1H), 7.0-7.5 (m,12H), 7.72 (dd,1H), 8.1-8.2 (m,2H), 8.97 (dd,1H)

Example 38

5-[N-Methyl-(3-(4-dibenzosuberane-5-yl)propionamide)]quinoline

Following the same procedure as in Example 37, 474 mg of 5-(methylamino)quinoline was reacted with 850 mg of 3-chloropropionyl chloride. The reaction product was reacted and treated with 834 mg of N-(dibenzosuberane-5-yl)piperazine synthesized in Example 2-(a) in an ethanol solvent in accordance with the same procedure as in Example 2-(a), in order to obtain 1.02 g of 5-[N-methyl-(3-(4-dibenzosuberanylpiperazine-1-yl)-propionamide)]quinoline.

IR νcm^{-1} (KBr): 3400, 2900, 2500, 1650, 1590, 1410, 1120

NMR δppm ($CDCl_3$): 1.7 (br,1H), 1.8-2.4 (m,12H), 2.5-2.6 (m,2H), 2.6-2.9 (m,2H), 3.34 (s,3H), 3.86 - (s,1H), 3.8-4.0 (m,2H), 7.0-7.7 (m,13H), 8.1-8.15 (m,2H), 8.98 (dd,1H)

Example 39

5-[N-Acetyl-(2-acetoxy-3-(4-diphenylmethylpiperazine-1-yl)propylamino)]quinoline.

In 4.5 g of acetic anhydride was dissolved 1.0 g of 5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxypropylamino]quinolinesynthesized in Example 27, and the liquid was then allowed to stand overnight. Afterward, the liquid was poured into an aqueous sodium bicarbonate solution, and it was then extracted with methylene chloride. The extract was dried with anhydrous magnesium sulfate and then concentrated, and the residue was purified through a silica gel column chromatograph by the use of ethyl acetate as an effluent solvent to obtain 1.05 g of the desired compound.

NMR δppm ($CDCl_3$): 1.69 (s,3H), 1.77 (s,3H), 2.1-2.7 (m,8H), 3.37 (dd,1H), 3.69 (dd,1H), 4.10 (s,1H), 3.34 (dd,1H), 3.61 (dd,1H), 4.61 (dd,1H)

Example 40

5-[N-Acetyl-(3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxypropylamino)]quinoline

In a mixed solvent of 10 ml of methanol and 5 ml of water were dissolved 0.55 g of 5-[N-acetyl-(2-acetoxy-3-(4-diphenylmethylpiperazine-1-yl)propylamino)]quinoline and 0.5 g of potassium carbonate, and the liquid was allowed to stand at room temperature overnight. The liquid was extracted with methylene chloride, and the extract was then dried with anhydrous magnesium sulfate and was concentrated to obtain 0.5 g of the desired compound.

NMR δppm ($CDCl_3$): 1.74 (s,3H), 2.1-2.9 (m,10H), 3.4-3.6 (m,1H), 3.8-4.2 (m,3H), 7.1-7.8 (m,13H), 8.1-8.3 (m,2H), 8.96-8.99 (m,1H)

Example 41

2-Chloro-5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxypropoxy]quinoline

Following the same procedure as in Example 23-(c), reaction and treatment were carried out using 1 g of 2-chloro-5-hydroxyquinoline and 2.88 g of 4-(3-chloro-2-hydroxypropyl)-1-diphenylmethylpiperazine synthesized in Example 23-(b), in order to obtain 1.39 g of 2-chloro-5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxypropoxy]quinoline.

NMR δppm (DMSO-d_6): 2.2-2.4 (m,4H), 2.4-2.7 (m,6H), 3.9-4.3 (m,4H), 4.91 (s,1H), 6.9-7.7 (m,14H), 8.64 (d,1H)

Example 42

5-[3-(4-Diphenylmethylpiperazine-1-yl)-2-hydroxypropoxy]-2-methoxyquinoline

Following the same procedure as in Example 23-(c), reaction and treatment were carried out using 0.6 g of 5-hydroxy-2-methoxyquinoline and 1.93 g of 4-(3-chloro-2-hydroxypropyl)-1-diphenylmethylpiperazine synthesized in Example 23-(b), in order to obtain 1.2 g of 5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxypropoxy]-2-methoxyquinoline.

NMR δppm (DMSO-d_6): 2.2-2.7 (m,4H), 2.4-2.7 (m,6H), 3.9-4.15 (m,6H), 4.19 (s,1H), 4.83 (s,1H), 6.75-6.9 (m,2H), 7.05-7.55 (m,12H), 8.46 (d,1H)

Example 43

5-[3-(4-Diphenylmethylpiperazine-1-yl)-2-hydroxypropoxy]isoquinoline

(a) With 40 ml of acetone were mixed 3.55 g of 5-hydroxyisoquinoline, 3.4 g of epichlorohydrin and 5.0 g of potassium carbonate, and the liquid was then heated under reflux for 6 hours. After the removal of insoluble substances, the solvent was distilled off, and the resultant residue was purified through a silica gel column chromatograph. On allowing an effluent solvent of chloroform:methanol = 100:1 to flow therethrough, 5-(2,3-epoxypropoxy)isoquinoline which was the desired product was obtained in an oily state in an amount of 1.6 g.

IR νcm^{-1} (liq. film): 3480, 2920, 1670, 1580, 1490, 1390, 1280, 1250

(b) In 20 ml of ethanol were dissolved 0.8 g of the above obtained epoxy compound and 1.0 g of N-diphenylmethylpiperazine, and the liquid was then heated under reflux for 2 hours. After the reaction, the solvent was distilled off, and the resultant residue was purified through a silica gel column chromatograph. On allowing an effluent solvent of chloroform:methanol = 50:1 to flow therethrough, 5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxypropoxy]isoquinoline which was the intended product was obtained in an powdery state in an amount of 0.7 g.

IR νcm^{-1} (KBr): 3420, 2820, 1620, 1580, 1490, 1450

NMR δppm ($CDCl_3$): 2.2-3.0 (m,10H), 3.8 (s,1H), 4.15 (s,2H), 4.25 (s,2H), 6.9-7.8 (m,13H), 8.0 (d,1H), 8.5 (d,1H), 9.2 (d,1H)

Example 44

5-[3-(4-(Dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxypropoxy]isoquinoline

In 20 ml of ethanol were dissolved 0.93 g of the epoxy compound prepared in Example 43-(a) and 1.29 g of the piperazine compound prepared in Example 2-(a), and the liquid was then heated under reflux for 2 hours. After the reaction, the solvent was distilled off, and the resultant residue was purified through a silica gel column chromatograph. On allowing an effluent solvent of chloroform:methanol = 50:1 to flow therethrough, the desired product 5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxypropoxy]isoquinoline was obtained in an powdery state in an amount of 1.14 g.

IR νcm^{-1} (KBr): 3400, 2920, 2800, 1580, 1490, 1430, 1390, 1280, 1110

NMR δppm ($CDCl_3$): 2.1-3.0 (m,12H), 3.6-4.4 (m,7H), 6.9-7.6 (m,11H), 8.0 (d,1H), 8.5 (m,1H), 9.15 (s,1H)

Example 45

5-[3-(4-Diphenylmethylhomopiperazine-1-yl)-2-hydroxypropoxy]isoquinoline

In 20 ml of ethanol were dissolved 0.74 g of the epoxy compound prepared in Example 43-(a) and 0.97 g of N-diphenylmethylhomopiperazine,and the liquid was then heated under reflux for 2 hours. After the reaction, the solvent was distilled off, and the resultant residue was purified through a silica gel column chromatograph. On allowing an effluent solvent of chloroform:methanol = 50:1 to flow therethrough, the desired product 5-[3-(4-diphenylmethylhomopiperazine-1-yl)-2-hydroxypropoxy]isoquinoline was obtained in an powdery state in an amount of 1.04 g.

NMR δppm ($CDCl_3$): 1.8 (t,2H), 2.3-3.3 (m,10H), 4.0 (s,1H), 4.15 (s,3H), 4.55 (s,1H), 6.8-7.7 (m,13H), 8.0 (d,1H), 8.5 (dd,1H), 9.15 (s,1H)

Example 46

8-[3-(4-Diphenylmethylpiperazine-1-yl)-2-hydroxypropoxy]isoquinoline

In 15 ml of dried THF were dissolved 80 mg of 8-hydroxyisoquinoline and 204 mg of 4-(3-(chloro-2-hydroxypropyl)-1-diphenylmethylpiperazine synthesized in Example 23-(b), and 68 mg of potassium t-butoxide was further added thereto, followed by stirring at room temperature for 20 hours. The reaction liquid was then poured into 15 ml of an aqueous saturated ammonium chloride solution, and extraction was then performed with 150 ml of methylene chloride. After drying with an anhydrous Glauber's salt, the solvent was distilled off, and the resultant residue was purified through a silica gel thin-layer chromatograph. Development was carried out by the use of an effluent solvent of chloroform:methanol = 25:1 for the purpose of separation and purification, with the result that 8-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxy-propoxy]-isoquinoline was obtained in an amount of 70 mg.

IR νcm^{-1} (KBr): 3400, 2800, 1570, 1450, 1390, 1280, 1120

NMR δppm ($CDCl_3$): 2.4-3.0 (m,10H), 3.7 (br,s,1H), 4.0-4.5 (m,4H), 6.96 (d,1H), 7.1-7.8 (m,13H), 8.56 (d,1H), 9.60 (s,1H)

Example 47

8-[3-(4-Diphenylmethylpiperazine-1-yl)-2-hydroxypropoxy]-quinoline

In 5 ml of dried THF were dissolved 200 mg of 8-hydroxyquinoline and 319 mg of the piperazine compound prepared in Example 23-(b), and 120 mg of potassium t-butoxide was further added thereto. The liquid was then stirred at room temperature for 5 days, and 20 ml of a 1 N aqueous sodium hydroxide solution was poured into the liquid, followed by extracting with 100 ml of methylene chloride. Afterward, the methylene chloride solution was washed with a dilute aqueous sodium hydroxide solution, and was then dried with an anhydrous Glauber's salt. After the solvent was distilled off, the residue was purified through a silica gel column chromatograph. On allowing an effluent solvent of chloroform:methanol = 50:1 to flow therethrough, the desired product 8-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxypropoxy]-quinoline was obtained in a powdery state in an amount of 45 mg.

IR νcm^{-1} (KBr): 3350, 2800, 1500, 1450, 1320, 1110

NMR δppm ($CDCl_3$): 2.2-3.0 (m,10H), 4.1-4.8 (m,4H), 4.9 (br,s,1H), 7.0-7.8 (m,14H), 8.15 (dd,1H), 8.85 (d,d,1H)

Example 48

5-[3-(4-Diphenylmethylpiperazine-1-yl)-2-hydroxypropoxy]quinoxaline

In 20 ml of dried DMF was dissolved 1 g of 5-hydroxyquinoxaline, and 0.78 g of t-butoxypotassium was further added. Afterward, the liquid was heated with stirring at 50 °C for 30 minutes. After the reaction, 1.9 g of epichlorohydrin was added thereto, followed by heating and stirring at 90 °C for 3 hours. The solvent was distilled off under reduced pressure and water was then added to the resultant residue, and the liquid extracted with 50 ml of chloroform. The chloroform liquid was dried with an anhydrous Glauber's salt, followed by distilling off, and the residue was then purified through a silica gel column chromatograph. On allowing an effluent solvent of chloroform:methanol = 100:1 to flow therethrough, 0.28 g of 5-(2,3-ex-

poypropoxy)quinoxaline was obtained in an oily state. In 10 ml of ethanol were dissolved 0.28 g of this epoxy compound and 0.35 g of N-diphenylmethylpiperazine, and the liquid was then heated under reflux for 3 hours. After the reaction, the solvent was distilled off, and the resultant residue was then purified by means of a silica gel column chromatograph. On allowing a solvent of chloroform:methanol = 50:1 to flow therethrough, the desired compound 5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxypropoxy]quinoxaline was obtained in a powdery state in an amount of 0.12 g.

IR νcm^{-1} (KBr): 3360, 2980, 1600, 1560, 1480, 1460, 1440, 1290, 1100

NMR δppm ($CDCl_3$): 2.2-3.2 (m,10H), 3.8 (s,1H), 4.1-4.6 (m,4H), 7.0-8.0 (m,13H), 8.7-9.1 (m,2H)

Example 49

5-[3-(4-Diphenylmethylpiperazine-1-yl)-2-hydroxypropoxy]quinazoline

In 30 ml of dried DMF was dissolved 2 g of 5-hydroxyqunazoline, and 1.5 g of t-butoxypotassium was added thereto, followed by heating and stirring at 50 °C for 1 hour. To the reaction liquid was added 4 g of epichlorohydrin, and the liquid was then heated with stirring at 90 °C for 3 hours. The solvent was distilled off under reduced pressure, and the resultant residue was then purified by the use of a silica gel column chromatograph. On allowing an effluent solvent of chloroform:methanol = 100:1 to flow therethrough, 5-(2,3-epxoypropoxy)quinazoline was obtained in an oily state in an amount of 0.84 g. In 20 ml of ethanol were dissolved 0.84 g of this epoxy compound and 1.05 g of N-diphenylmethylpiperazine, and the liquid was then heated under reflux for 3 hours. After the reaction, the solvent was distilled off, and the resultant residue was then purified through the silica gel column chromatograph. On allowing the effluent solvent of chloroform:methanol = 50:1 to flow therethrough, the intended product 5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxypropoxy]quinazoline was obtained in a powdery state in an amount of 0.48 g.

IR νcm^{-1} (KBr): 3400, 2800, 1610, 1580, 1130

NMR δppm ($CDCl_3$): 2.2-3.0 (m,10H), 3.4 (br,s,1H), 2.0-2.3 (m,4H), 6.9-7.9 (m,13H), 9.28 (s,1H), 9.70 (s,1H)

Example 50

5-(3-[4-((4-Pyridyl)-phenylmethyl)piperazine-1-yl]-2-hydroxypropoxy)quinoline

Following the same procedure as in Example 1-(b), reaction and treatment were carried out using N-[(4-pyridyl)-phenylmethyl]piperazine to obtain the desired compound.

IR νcm^{-1} (KBr): 3350, 1620, 1590, 1410, 1370, 1270, 1100, 780

NMR δppm ($CDCl_3$): 2.3-3.9 (m,10H), 4.05-4.20 (m,3H), 4.25 (s,1H), 6.85 (d,1H), 7.2-7.4(m,8H), 7.58 (t,1H), 7.70 (d,1H), 8.50 (d,1H), 8.55 (d,1H), 2.89 (d,1H)

Example 51

2,4-Dimethyl-5-[3-((α,α-diphenylacetyl)piperazine-1-yl)-2-hydroxypropoxy]quinoline

Following the same procedure as in Example 1-(a) and (b), reaction and treatment were carried out using 2,4-dimethyl-5-hydroxyquinoline prepared in Example 5-(b) and N-(α,α-diphenylacetyl)piperazine in order to obtain the desired compound.

IR νcm^{-1} (KBr) (HCl salt): 3350 (br.), 1630, 1595, 1430, 1380, 1260, 1090, 1025, 735, 690

NMR 270 MHz ($CDCl_3$) δppm: 2.10-2.72 (m,5H), 2.63 (s,3H), 2.83 (s,3H), 3.30-3.60 (m,3H), 3.60-3.80 (m,2H), 4.00-4.20 (m,2H), 5.19 (s,1H), 6.75 (d,1H), 6.99 (s,1H), 7.20-7.40 (m,10H), 7.47 (tr,1H), 7.60 (d,1H)

Example 52

2-Trifluoromethyl-4-methyl-5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxypropoxy]quinoline

The same procedures as in Example 5-(a) and (b) were repeated with the exception that acetylacetone was replaced with α,α,α-trifuloroacetylacetone, in order to perform reaction and treatment, whereby 2-trifluoromethyl-4-methyl-5-hydroxyquinoline was obtained.

Furthermore, following the same procesures as in Example 1-(a) and (b), reaction and treatment were carried out using the thus prepared compound and N-(dipenzosuberane-5-yl)piperazine to obtain the desired compound.

IR νcm^{-1} (KBr): 2920, 2800, 1590, 1370, 1350, 1330, 1270, 1180, 1140, 750

NMR ($CDCl_3$) δppm: 2.20-2.90 (m,12H), 2.76 (s,3H), 3.90-4.25 (m,6H), 6.95-7.20 (m,9H), 7.55-7.75 (m,3H)

Example 53

2-Trifluoromethyl-4-methyl-5-[3-(4-(α,α-diphenylacetyl)piperazine-1-yl)-2-hydroxypropoxy]quinoline Following the same procedures as in Example 1-(a) and (b), reaction and treatment were carried out using 2-trifluoromethyl-4-methyl-5-hydroxyquinoline prepared in Example 54 and N-(α,α-diphenylacetyl)piperazine in order to obtain the desired compound.

IR νcm^{-1} (KBr): 1630, 1595, 1450, 1430, 1380, 1350, 1270, 1180, 1140

NMR ($CDCl_3$) δppm: 2.15-2.70 (m,6H), 2.77 (s,3H), 3.40-3.55 (m,2H), 3.65-3.80 (m,2H), 4.00-4.30 (m,3H), 5.20 (s,1H), 7.00 (d,1H, J = 7.41), 7.10-7.50 (m,10H), 7.60-7.80 (m,3H)

Examle 54

2-Trifluoromethyl-4-methyl-5-[3-(4-diphenylmethylpiperazine-1-yl)-2-hydroxypropoxy]quinoline

Following the same procedures as in Example 1-(a) and (b), reaction and treatment were carried out using 2-trifluoromethyl-4-methyl-5-hydroxyquinoline prepared in Example 54 and N-diphenylmethyl-piperazine in order to obtain the desired compound.

IR νcm^{-1} (KBr): 2800, 1595, 1450, 1380, 1350, 1330, 1270, 1180, 1140

NMR $\delta(CDCl_3)$ ppm: 2.20-2.90 (m,10H), 2.77 (s,3H), 4.00-4.35 (m,4H), 7.02 (d,1H, J = 7.92 Hz), 7.10-7.55 (m,10H), 7.55-7.80 (m,3H)

Example 55

5-(3-[4-(Bis(4-fluorophenyl)methyl)piperazine-1yl]-2-hydroxypropoxy)quinoline

Following the same procedure as in Example 1-(b), reaction and treatment were carried out using the epoxy compound prepared in Example 1-(a) and N-[bis-(4-fluorophenyl)methyl]piperazine in order to obtain the desired compound.

IR (KBr) νmax cm^{-1} (HCl salt): 3400, 1630, 1590, 1510, 1410, 1280, 1230

NMR δppm ($CDCl_3$): 2.1-2.9 (10H, bm), 4.1-4.2 (3H,m), 6.85-7.75 (12H,m), 8.55 (1H,dd), 8.9 (1H,dd)

Example 56

5-(3-[4-((4-Chlorophenyl)-phenylmethyl)piperazine-1-yl]-2-hydroxypropoxy)quinoline

Following the same procedure as in Example 1-(b), reaction and treatment were carried out using the epoxy compound prepared in Example 1-(a) and N-[(4-chlorophenyl)phenylmethyl]piperazine in order to obtain the desired compound.

IR (KBr) νmax cm^{-1} (HCl salt): 3400, 1630, 1590, 1410, 1380, 1280

NMR ($CDCl_3$) δppm: 2.17-2.93 (10H,bm), 4.1-4.3 (4H,m), 6.85 (1H,d), 7.16-7.74 (12H,m), 8.55 (1H,dd), 8.9 (1H,dd)

Example 57

5-(3-[4-(Bis-(4-methoxyphenyl)methyl)piperazine-1-yl]-2-hydroxypropoxy)quinoline

Following the same procedure as in Example 1-(b), reaction and treatment were carried out using the epoxy compound prepared in Example 1-(a) and N-[4-bis-(4-methoxyphenyl)methyl]piperazine in order to obtain the desired compound.

IR νmax cm^{-1} (KBr): 3400, 1635, 1610, 1595, 1510, 1410, 1280, 1250
NMR ($CDCl_3$) δppm: 2.34-2.76 (10H, bm), 3.75 (6H,s), 4.11-4.24 (4H,m), 6.80-6.87 (5H,m), 7.26-7.39 (5H,m), 7.55-7.71 (2H,m), 8.57 (1H,d), 8.89 (1H,dd)

Example 58

5-[3-(4-(Iminodibenzyl-5-carbonyl)piperazine-1-yl)-2-hydroxypropoxy]quinoline

Following the same procedure as in Example 1-(b), reaction and treatment were carried out using the epoxy compound prepared in Example 1-(a) and N-(iminodibenzyl-5-carbonyl)piperazine in order to obtain the desired compound.
IR νmax cm^{-1} (KBr) (HCl salt): 3400, 1640, 1600, 1490, 1415, 1380, 1280
NMR ($CDCl_3$) δppm: 2.3-2.4 (2H,m), 2.53-2.61 (4H,m), 3.15 (4H,s), 3.40 (4H,m), 4.10-4.22 (3H,m), 6.85 (1H,d), 7.09-7.71 (11H,m), 8.52 (1H,dd), 8.90 (1H,dd)

Example 59

2,4-Dimethyl-5-[3-(4-(iminodibenzyl-5-carbonyl)piperazine-1-yl)-2-hydroxypropoxy]quinoline

Following the same procedure as in Example 1-(b), reaction and treatment were carried out using the epxoy compound prepared in Example 5 and N-(iminodibenzyl-5-carbonyl)piperazine in order to obtain the desired compound.
IR νmax cm^{-1} (KBr) (HCl salt): 3400, 3240, 1640, 1600, 1480, 1440, 1390, 1270, 1260
NMR δppm ($CDCl_3$): 1.8-2.15 (1H,m), 2.26-2.40 (2H,m), 2.50-2.60 (4H,m), 2.64 (3H,s), 2.84 (3H,s), 3.16 (4H,s), 3.40 (4H,s), 4.01-4.20 (3H,m), 6.77 (1H,d), 6.99 (1H,s), 7.09-7.62 (10H,m)

Example 60

5-[3-(N'-(Dibenzosuberane-5-yl)ethylenediamino)-2-hydroxypropoxy]quinoline

Following the same procedure as in Example 1-(b), reaction and treatment were carried out using the epxoy compound prepared in Example 1-(a) and N-(dibenzosuberane-5-yl)ethylenediamine in order to obtain the desired compound.
IR νmax cm^{-1} (KBr) (HCl): 3400, 2920, 1630, 1590, 1410, 1380, 1280, 1100
NMR δppm ($CDCl_3$): 2.20-2.59 (2H, bs), 2.60-3.0 (8H,m), 3.56-3.72 (2H,m), 4.04-4.25 (3H,m), 4.77 (1H,s), 8.82 (1H,d), 7.08-7.75 (11H,m), 8.53 (1H,dd), 8.87 (1H,dd)

Example 61

5-[3-(N,N'-Dimethyl-N'-(dibenzosuberan-5-yl)ethylenediamino-2-hydroxypropoxy]quinoline

Following the same procedure as in Example 1-(b), reaction and treatment were carried out using the epoxy compound prepared in Example 1-(a) and N,N'-dimethyl-N'-(dibenzosuberane-5-yl)ethylenediamine in order to obtain the desired compound.
IR νmax cm^{-1} (KBr) (HCl salt): 3400, 2920, 1630, 1590, 1470, 1410, 1370, 1280, 1100
NMR δppm ($CDCl_3$): 2.13 (6H,d), 2.4-2.55 (5H,m), 2.56-2.90 (3H,m), 3.90-4.20 (6H,m), 6.85 (1H,d), 6.98-7.75 (11H,m), 8.57 (1H,dd), 8.92 (1H,dd)

Example 62

2-Methylthio-5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxypropoxy]quinoline

An epoxy compound was prepared from 2-methylthio-5-hydroxyquinoline in accordance with the same procedure as in Example 1-(a), and reaction and treatment were then carried out using this epoxy compound and N-(dibenzosuberane-5-yl)piperazine to obtain the desired compound.
IR νcm^{-1} (KBr) (HCl salt): 1615, 1600, 1575, 1480, 1440, 1390, 1335, 1285, 1250, 1125
NMR δppm ($CDCl_3$): 2.20-2.85 (m,12H), 2.67 (s,3H), 3.85-4.20 (m,6H), 6.74 (d,1H,J = 8.9), 6.95-

7.30 (m,9H), 7.40-7.55 (m,2H), 8.26 (d,1H,J = 8.9)

Example 63

2-Methylthio-5-[3-(4-(α,α-diphenylacetyl)piperazine-1-yl)-2-hydroxypropoxy]quinoline

An epoxy compound was prepared from 2-methylthio-5-hydroxyquinoline in accordance with the same procedure as in Example 1-(a), and reaction and treatment were then carried out using this epoxy compound and N-(α,α-diphenylacetyl)piperazine to obtain the desired compound.

IR (KBr) νcm^{-1} (HCl salt): 1630, 1580, 1440, 1420, 1390, 1250, 1130, 1070, 1020

NMR 270 MHz ($CDCl_3$) δppm: 2.15-2.25 (m,1H), 2.35-2.70 (m,5H), 2.68 (s,3H), 3.40-3.55 (m,2H), 3.65-3.80 (m,2H), 4.05-4.20 (m,3H), 6.75 (d,1H,J = 8.4), 7.15-7.35 (m,11H), 7.45-7.55 (m,2H), 8.38 (d,1H,J = 8.91)

Example 64

2,4-Dimethyl-5-[3-(N,N'-dimethyl-N'-(dibenzosuberane-5-yl)ethylenediamino)-2-hydroxypropoxy]quinoline

Following the same procedure as in Example 1-(b), reaction and treatment were carried out using the epoxy compound prepared in Example 5 and N,N'-dimethyl-N'-(dibenzosuberane-5-yl)ethylenediamine in order to obtain the desired compound.

NMR ($CDCl_3$) δppm: 2.12 (6H,d), 2.40-2.6 (5H,m), 2.65 (3H,s), 2.70-2.90 (5H,m), 3.93-4.10 (6H,m), 6.77 (1H,d), 7.00-7.20 (9H,m), 7.45-7.65 (2H,m)

Example 65

2,4-Dimethyl-5-[3-(4-diphenylmethylenepiperizine-1-yl)-2-hydroxypropoxy]quinoline

Following the same procedure as in Example 1-(b), reaction and treatment were carried out using the epoxy compound prepared in Example 5 and 4-diphenylmethylenepiperizine to obtain the desired compound.

IR (KBr) νmax cm^{-1} (HCl salt): 3380, 2900, 2640, 1630, 1600, 1470, 1440, 1380, 1270

NMR ($CDCl_3$) δppm: 1.74-1.97 (1H,bm), 2.35-2.60 (6H,m), 2.62-2.95 (10H,m), 4.05-4.30 (3H,m), 6.80 (1H,d), 7.00 (1H,s), 7.10-7.35 (10H,m), 7.45-7.65 (2H,m)

Example 66

5-[3-(10,11-Dihydro-N-methyl-5H-dibenzo[a,d]-cycloheptene-$\Delta^{5,\gamma}$-propylamino)-2-hydroxypropoxy]quinoline

Following the same procedure as in Example 1-(b), reaction and treatment were carried out using the epoxy compound prepared in Example 1-(a) and hydroxydibenzosuberane in order to obtain the desired compound.

IR (KBr) νmax cm^{-1} (HCl salt): 3360, 2640, 1630, 1590, 1475, 1410, 1370, 1270, 1100

NMR ($CDCl_3$) δppm: 1.45-2.05 (5H, bm), 2.28 (3H,s), 2.31-2.85 (6H,m), 3.2-3.5 (1H,bm), 4.05-4.35 (3H,m), 6.8-7.76 (12H,m), 8.52-8.58 (1H,m), 8.89-8.93 (1H,m)

Example 67

5-[3-(3,3-Diphenylpropylamino)-2-hydroxypropoxy]quinoline

Following the same procedure as in Example 1-(b), reaction and treatment were carried out using the epoxy compound prepared in Example 1-(a) and 3,3-diphenylpropylamine to obtain the desired compound.

IR (KBr) νcm^{-1}: 1610, 1580, 1490, 1460, 1400, 1360, 1315, 1270, 1200, 1170, 1140

NMR 270 ($CDCl_3$) δppm: 2.43-2.60 (m,2H), 2.80-3.15 (m,3H), 4.90-5.20 (m,5H), 6.67 (d,1H,J = 7.42), 7.05-7.40 (m,11H), 7.45-7.80 (m,2H), 8.53 (d,1H,J = 8.4), 8.80-8.95 (m,1H)

Example 68

5-[3-(2,2-Diphenylethylamino)-2-hydroxypropoxy]quinoline

Following the same procedure as in Example 1-(b), reaction and treatment were carried out using the epoxy compound prepared in Example 1-(a) and 2,2-diphenylethylamine in order to obtain the desired compound.

IR (KBr) νcm^{-1} (HCl salt): 1620, 1580, 1480, 1440, 1400, 1370, 1270, 1200, 1170, 1140

NMR 270 ($CDCl_3$) δppm: 2.85-3.40 (m,3H), 4.00-4.28 (m,5H), 6.82 (d,1H,J=7.42), 7.05-7.40 (m,1H), 7.52-7.72 (m,2H), 8.45-8.55 (m,1H), 8.85-8.90 (m,1H)

Example 69

2-Methylsufonyl-5-[3-(4-(dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxypropoxy]quinoline

An epoxy compound was prepared from 2-methylsulfonyl-5-hydroxyquinoline in accordance with the same procedure as in Example 1-(a), and reaction and treatment were then made using the thus prepared epoxy compound and N-(dibenzosuberane-5-yl)piperazineto obtain the desired compound.

IR (KBr) νcm^{-1}: 1640, 1610, 1575, 1465, 1450, 1300, 1270, 1160, 1140, 1120

NMR ($CDCl_3$) δppm: 2.20-2.90 (m,12H), 3.35 (s,3H), 3.90-4.30 (m,6H), 6.95-7.25 (m,9H), 7.66-7.82 (m,2H), 8.07 (d,1H,J=8.4), 8.83 (d,1H,J=8.91)

Example 70

5-[3-(4-(Xanthene-9-yl)piperazine-1-yl)-2-hydroxypropoxy]quinoline

Following the same procedure as in Example 1-(b), reaction and treatment were carried out using the epoxy compound prepared in Example 1-(a) and N-(xanthene-9-yl)piperazine.

IR (KBr) νcm^{-1}: 3400, 2800, 1580, 1460, 1440, 1240, 980, 740

NMR δppm ($CDCl_3$): 2.3-2.7 (m,10H), 4.0-4.15 (m,3H), 4.83 (s,1H), 6.81 (d,1H), 7.1-7.4 (m,9H), 7.56 (t,1H), 7.67 (d,1H), 8.52 (d,1H), 8.88 (d,1H)

Example 71

5-[3-(N-Methyl-3-(5-iminodibenzyl)propylamino)-2-hydroxypropoxy]quinoline

Following the same procedure as in Example 1-(b), reaction and treatment were carried out using an epoxy compound prepared in Example 1-(a) and desipramine in order to obtain the desired compound.

IR KBr νmax cm^{-1} (HCl salt): 3380, 2640, 1630, 1590, 1485, 1470, 1410, 1380, 1280, 1110

NMR ($CDCl_3$) δppm: 1.65-1.76 (2H,m), 2.18 (3H,s), 2.37-2.58 (4H,m), 3.11 (4H,s), 3.67-3.86 (2H,m), 3.98-4.10 (3H,m), 6.74-6.86 (3H,m), 6.97-7.08 (6H,m), 7.27-7.32 (1H,m), 7.48-7.67 (2H,m), 8.42-8.50 (1H,m), 8.81-8.84 (1H,dd)

Example 72

5-[3-(4-Diphenylmethylpiperazine-1-yl)-2-hydroxypropylthio]qunoline

In 10 ml of chloroform were dissolved 1.2 g of 4-(3-chloro-2-hydroxypropy)-1-diphenylmethylpiperazine prepared in Example 23-(b) and 220 mg of 5-mercaptoquinoline, and 311 mg of DBU was further added thereto. Afterward, the liquid was allowed to stand at room temperature for 12 days. The reaction liquid was poured into 20 ml of water and was then extracted twice with methylene chloride. The resultant organic layer was separated, then dried with an anhydrous Glauber's salt, and was distilled off under reduced pressure. The resultant residue was purified through a silica gel chromatograph (an AcOEt effluent solvent was used) in order to obtain 130 mg of the desired compound.

IR max νcm^{-1} (KBr): 3300, 2520, 1620, 1580, 1420, 1390, 1360, 1290, 1070, 910

NMR δppm ($CDCl_3$): 2.3-2.7 (m,12H), 3.8-3.9 (m,1H), 4.21 (s,1H), 7.1-7.7 (m,13H), 8.00 (dd,1H), 8.75 (dd,1H), 8.94 (dd,1H)

Example 73

5-[3-(4-(Dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxy-propylthio]quinoline

The same procedure as in Example 23-(b) was repeated with the exception that diphenylmethylpiperazine was replaced with 4-(dibenzosuberane-5-yl)piperazine, in order to prepare 4-(3-chloro-2-hydroxypropyl)-1-(dibenzosuberane-5-yl)piperazine, and reaction and treatment were then carried out using 932 mg of the thus prepared piperazine compound and 270 mg of 5-mercaptoquinoline in accordance with the same procedure as in Example 72, so that 220 mg of the desired compound was obtained.

IR max νcm^{-1} (KBr): 3300, 2500, 1580, 1390, 1360, 1300, 1070, 860, 760, 650, 620

NMR δppm ($CDCl_3$): 2.1-2.7 (m,12H), 2.7-2.9 (m,2H), 3.8-4.1 (m,4H), 7.0-7.8 (m,11H), 8.00 (d,1H), 8.75 (dd,1H), 8.93 (dd,1H)

Example 74

5-[3-(4-(Dibenzosuberane-5-yl)piperazine-1-yl)-2-hydroxypropoxy]-2,4-bis(trifluoromethyl)quinoline

(a) Following the same procedure as in Example 1-(a), reaction and treatment were carried out using 0.38 g of 2,4-bis(trifluoromethyl)-5-hydroxyquinoline, in order to obtain 0.18 g of 5-(2,3-epoxy)propoxy-2,4-bis(trifluoromethyl)quinoline.

NMR δppm ($CDCl_3$): 2.7-2.8 (m,1H), 2.9-3.0 (m,1H), 3.4-3.5 (m,1H), 4.1-4.4 (m,2H), 7.19 (d,1H), 7.81 (t,1H), 7.96 (d,1H), 8.08 (s,1H)

(b) Following the same procedure as in Example 1-(b), reaction and treatment were carried out using 0.18 g of the above synthesized epoxy compound and 0.16 g of (dibenzosuberane-5-yl)-piperazinesynthesized in Example 2-(a), in order to obtain 0.3 g of 5-[3-(4-(dibenzosuberane-5-yl)-piperazine-1-yl)-2-hydroxypropoxy]-2,4-bis(trifluoromethyl)quinoline.

NMR δppm ($CDCl_3$): 2.16-2.90 (m,12H), 3.9-4.3 (m,6H), 7.0-7.3 (m,10H), 7.80 (t,1H), 7.94 (d,1H), 8.05 (s,1H)

Example 75

5-[3-(4-(Dibenzosuberene-5-ylidene)piperidine-1-yl)-2-hydroxypropoxy]quinoline

Following the same procedure as in Example 1-(b), reaction and treatment were carried out using 1.66 g of 4-(dibenzosuberene-5-ylidene)piperidine and 1.65 g of epoxy compound synthesized in Example 1-(a), in order to obtain 1.32 g of 5-[3-(4-(dibenzosuberene-5-ylidene)piperidine-1-yl)-2-hydroxypropoxy]quinoline.

IR νcm^{-1} (KBr): 3400, 2700, 1645, 1590, 1410

NMR δppm ($CDCl_3$): 2.1-2.9 (m,10H), 3.9-4.2 (m,3H), 6.78 (d,1H), 6.86 (s,2H), 7.1-7.3 (m,8H), 7.50 (t,1H), 7.63 (d,1H), 8.47 (d,1H), 8.81 (d,1H)

Example 76

5-[2-Hyroxy-3-(4-(5-hydroxydibenzosuberane-5-yl)piperidine-1-yl)propoxy]quinoline

Following the same procedure as in Example 1-(b), reaction and treatment were carried out using 0.78 g of 4-(5-hydroxydibenzosuberane-5-yl)piperidine and 0.80 g of epoxy compound synthesized in Example 1-(a), in order to obtain 0.99 g of 5-[2-hydroxy-3-(4-(5-hydroxydibenzosuberane-5-yl)piperidine-1-yl)-propoxy]quinoline.

IR νcm^{-1} (KBr): 3400, 2700, 1630, 1590, 1410, 1280, 1105, 790

NMR δppm ($CDCl_3$): 1.2-2.6 (m,12H), 2.9-3.05 (m,2H), 3.43-3.52 (m,2H), 4.0-4.1 (m,1H), 4.15 (d,2H), 6.82 (d,1H), 7.0-7.2 (m,6H), 7.33 (dd,1H), 7.55 (t,1H), 7.65 (d,1H), 7.80 (d,2H), 8.51 (d,1H), 8.86 (dd,1H)

Example 82

5-[3-(4-(Diphenylmethylene)piperidine-1-yl)propoxy]quinoline

Following the same procedure as in Example 1-(b), reaction and treatment were carried out using 0.68 g of 4-(diphenylmethylene)piperidine and 0.55 g of quinoline compound synthesized in Example 32-(a), in order to obtain 0.59 g of 5-[3-(4-(diphenylmethylene)piperidine-1-yl)propoxy]quinoline.

IR νcm^{-1} (KBr): 3400, 2920, 1630, 1590, 1460, 1410, 1375, 1280

NMR δppm ($CDCl_3$): 2.1-2.7 (m, 12H), 4.27 (t,2H), 6.85 (d,1H), 7.1-7.4 (m,11H), 7.56-7.7 (m,2H), 8.59 (dd,1H), 8.9 (dd,1H)

Experimental Example 1:

Potentiating effect of the compounds on incorporation of anticancer drugs into drug-resistant cancer cells

Adriamycin resistant strain 2780AD cells of human ovarian cancer A2780 cells (A. M. Rogan et al., Science 224, 994-996, 1984) were suspended at a concentration of 1 x 10^6 /ml in RPMI-1640 medium supplemented with 5 % fetal calf serum, and 1 ml of the cancer cell suspension was dispensed into each well of a multi-well culture plate (24 wells, 16 cm in diameter) and then incubated at 37 • C in an atmosphere of 5% CO_2. After 24 hours incubation, the medium in each well was replaced by 0.5 ml of RPMI-1640 medium supplemented containing 20 nM ^{3}H-vincristine (1 x 10^4dpm/pmol), 5 % fetal calf serum and 10 mM Hepes buffer. Five microliters of a solution of the compound to be tested, which had been dissolved in DMSO and diluted with serine-phosphate buffer (at a concentration of 1.0 microgram/ml or 10.0 micrograms/ml), was added to each well and the incubation was continued at 37 • C in 5 % CO_2 for 2 hours. The resultant cells were washed in cold saline-phosphate buffer. In each well was added 0.5 ml of 0.2 N NaOH, and the resulting cell suspension in each well was independently transferred into a vial and then heated in a water bath at 56 • C for 30 - 60 minutes to dissolve the cells. After adding 4 ml of acid aquazole 2, the amount of ^{3}H-vincristine incorporated into the cells was determined by a fluid scintillation counter.

The potentiating effect was expressed by percentage (%) of the amount of vincristine incorporated into the cells treated with the test compound compared to that incorporated into the control cells without treatment. The results are shown in Table 1.

Experimental Example 2:

Potentiating effect of the compounds on activity of anticancer drugs

Adriamycin resistant strain K562/ADM cell's of human myeloleukemia K562 cells were suspended at a concentration of 2 x 10^4 /ml in RPMI-1640 medium supplemented with 5 % fetal calf serum, and 2 ml of the cancer cell suspension was dispensed into each tube (12 x 75 mm) and then incubated at 37 • C in 5% CO_2. After 6 hours incubation, vincristine (0 - 3,000 ng/ml) and the test compound (0.3, 1 or 3 ng/ml) were added, and the incubation was continued at 37 • C in 5 % CO_2 for 2 hours. The cell suspension was added to 9.5 ml of ISTON II, and the number of cells were counted by a Coulter counter to estimate the vincristine concentration at which 50 % growth was inhibited, IC_{50} (ng/ml).

Two cases from the results of the experiments, IC_{50} value and potentiating effect, with the compounds given in Table 1 as set forth are given in Table 2. Likewise, the potentiating effect on the activity of drugs was observed with the other compounds in Table 1 (data omitted).

Experimental Example 3

Potentiating effect on the activity of anticancer-drugs on mice having vincristine-resistant mouse leukemia

Vincristine-resistant strain P388/VCR cells of mouse leukemia P388 cells (1 x 10^6) were peritoneally transplanted into female CDFI mice, and then vincristine and the test compound given in Table 1 in combination were peritoneally administered once a day for 5 days.

Survival of animals was observed, and percentage (%) of surviving days of the animals administered with the test compound to those of the control animals, (T/C), were calculated. The results are partially shown in Tables 3(a) - 3(f).

A similar effect on survival was observed with the other compounds in Table 1 (data omitted).

Table 1

Compound (Example #)	^{3}H-vincristine accumulation (%)	
	Concentration of compound (µg/ml)	
	1	10
None (Control)	100	100
1	717	747
2	663	709
3	731	774
4	438	770
5	732	1040
6	1035	1135
7	972	1040
8	394	863
9	721	947
10	642	932
11	735	1073
12	568	831
13	517	805
14	119	871
15	840	1072
16	850	982
17	730	1040
18	743	761
19	374	524
20	794	1054
21	727	745
22	723	743
23	723	1604
24	146	931
25	858	1376
26	177	1111
27	1146	1239
28	1705	1147
29	246	1161
30	597	1083
31	428	799
32	816	1413
33	447	1081
34	785	1034
35	654	627
36	821	716
37	549	1000
38	378	819
39	236	908
40	259	1017
41	584	1231

Table 1 (continued)

Compound (Example #)	^{3}H-vincristine accumulation (%)	
	Concentration of compound (μg/ml) 1	10
None (control)	100	100
42	624	1011
43	531	1297
44	636	934
45	307	982
46	322	879
47	213	612
48	559	668
49	534	798
50	379	910
51	658	794
52	253	777
53	452	756
54	321	735
55	572	732
56	619	843
57	561	685
58	643	760
59	519	602
60	525	1125
61	773	1130
62	425	900
63	297	985
64	488	1071
65	730	1065
66	671	1097
67	738	941
68	252	960
69	501	921
70	112	144
72	626	1024
73	587	1064
74	130	304
75	1019	1192
76	943	1077
77	841	963
78	942	1143
79	992	1232
80	667	1273
81	957	1263
82	159	878

Table 2

Compound (Example #)	IC_{50} (ng/ml)*1			
	Concentration of compound (μg/ml)			
	0	0.3	1	3
1	655	4.3(151.2)*2	1.9(342.1)	1.5(433.3)
2	655	2.0(330.3)	1.7(388.0)	1.2(550.0)

*1 Vincristine concentration at which 50 % of the growth of adriamycin-resistant human myeloleukemia K562 cells (K562/ADM) was inhibited.

*2 Values in parentheses, which indicate effect in potentiating vincristine activity by test compounds, are multiples of the control. The calculation was made by dividing the value of IC_{50} for the individual test compound by that for the control (without test compound), 655.

Table 3-(a)

Compound		Vincristine (μg/kg)	Average surviving period (days)	T/C* (%)
Example #	Concentration (mg/kg)			
Control	(none)	0	11.2 ± 1.0	100
None	(none)	100	11.5 ± 0.5	103
1	3	100	12.4 ± 0.2	111
1	10	100	12.2 ± 0.4	109
1	30	100	12.8 ± 0.4	114
2	3	100	12.6 ± 0.2	113
2	30	100	15.2 ± 0.7	136
44	10	100	12.5 ± 0.0	112
44	30	100	13.8 ± 1.0	123

* Rate of life prolongation

Table 3-(b)

Compound		Vincristine (μg/kg)	Average surviving period (days)	T/C* (%)
Example #	Concentration (mg/kg)			
Control	(none)	0	10.5 ± 0.6	100
None	(none)	100	11.5 ± 0.4	110
6	30	100	13.4 ± 0.7	128
7	30	100	12.9 ± 0.5	123
11	30	100	12.1 ± 0.5	115
15	30	100	12.3 ± 0.4	117
16	30	100	13.9 ± 1.4	132
18	30	100	13.8 ± 0.4	131
22	30	100	13.9 ± 0.4	132

* Rate of life prolongation

Table 3-(c)

Compound		Vincristine (μg/kg)	Average surviving period (days)	T/C* (%)
Example #	Concentration (mg/kg)			
Control	(none)	0	10.3 ± 0.7	100
None	(none)	100	10.8 ± 0.8	105
27	30	100	12.3 ± 0.3	119
5	30	100	12.8 ± 0.8	124
32	30	100	11.3 ± 0.4	110
17	30	100	11.8 ± 1.1	115
35	30	100	11.9 ± 0.7	116
36	30	100	12.6 ± 0.9	122
20	30	100	13.7 ± 1.0	133
21	30	100	12.5 ± 0.6	121

* Rate of life prolongation

Table 3-(d)

Compound		Vincristine (μg/kg)	Average surviving period (days)	T/C* (%)
Example #	Concentration (mg/kg)			
Control	(none)	0	11.0 ± 0.4	100
None	(none)	100	10.7 ± 0.4	97
3	30	100	11.0 ± 0.6	100
4	30	100	11.8 ± 0.4	107
41	30	100	13.2 ± 1.8	120
42	30	100	13.9 ± 2.4	126
10	30	100	12.3 ± 1.4	112
12	30	100	12.5 ± 0.5	114
13	30	100	15.3 ± 0.5	139
34	30	100	10.8 ± 0.8	98

* Rate of life prolongation

Table 3-(e)

Compound		Vincristine (μg/kg)	Average surviving period (days)	T/C* (%)
Example #	Concentration (mg/kg)			
Control	(none)	0	10.6 ± 0.4	100
None	(none)	100	11.3 ± 0.5	107
8	30	100	12.2 ± 0.6	115
9	30	100	14.2 ± 0.6	134
51	30	100	11.8 ± 0.8	111
53	30	100	12.7 ± 0.3	120
55	30	100	13.1 ± 0.4	124
56	30	100	13.8 ± 1.8	130
57	30	100	13.2 ± 1.2	125
58	30	100	12.4 ± 0.7	117
59	30	100	11.5 ± 0.3	108

* Rate of life prolongation

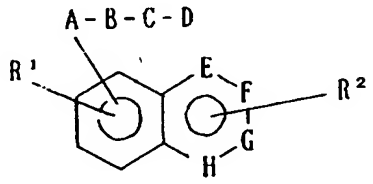
Table 3-(f)

Compound		Vincristine (μg/kg)	Average surviving period (days)	T/C* (%)
Example #	Concentration (mg/kg)			
Control	(none)	0	10.7 ± 1.0	100
None	(none)	100	11.3 ± 0.6	106
75	30	100	13.8 ± 1.2	129
76	30	100	12.8 ± 0.8	120
78	30	100	14.3 ± 0.6	134
79	30	100	13.2 ± 0.9	123
80	30	100	11.2 ± 1.4	105
81	30	100	13.5 ± 0.5	126
82	30	100	13.0 ± 0.7	121

*Rate of life prolongation

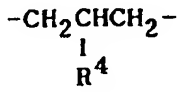
Claims

1. A compound of the general formula [I]

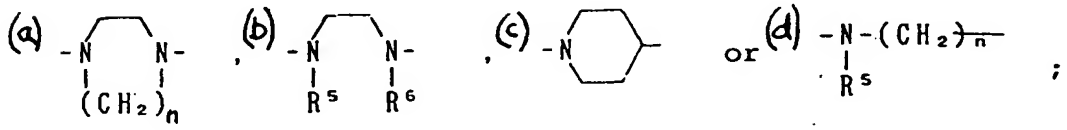


[I]

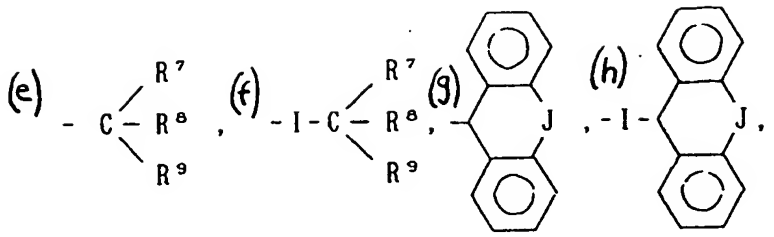
in which A represents an oxygen or sulfur atom or a methylene, amino or -NR^3 group, which is bound to any available position on the condensed benzene ring; B represents -$(CH_2)_n$-,

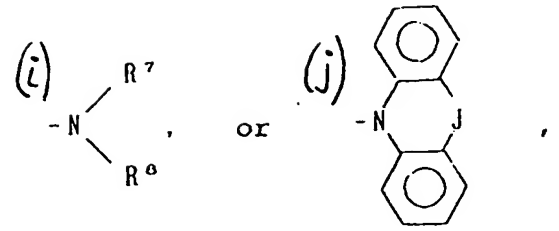


or -$CO(CH_2)_n$-; C represents

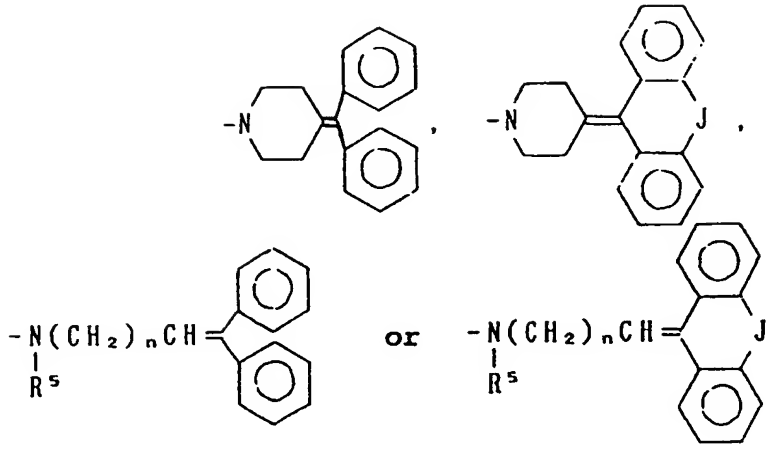


D represents





C and D can together form



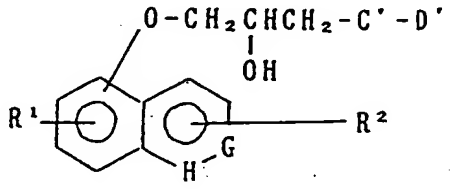
E, F, G and H each independently represent a carbon or nitrogen atom, provided that either one or two of them is nitrogen, R^1 and R^2 each independently represent a hydrogen or halogen atom, a C_{1-4} alkyl, amino group, substituted amino group, a C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylsulfonyl, trifluoromethyl, cyano, nitro, amide or hydroxy group, wherein R^1 and R^2 may be on any position available on the condensed ring or one each on each of the rings or both on the same ring of which the condensed ring is formed; R^3 represents a hydrogen atom or a C_{1-4} alkyl or acyl group; R^4 represents a hydroxyl, lower alkylamino (where alkyl is C_{1-4}), C_{1-4} alkoxyl or C_{1-2} acyloxy group; R^5 and R^6 each independently represent a hydrogen atom or a C_{1-4} alkyl or hydroxyalkyl group; R^7, R^8 and R^9 each independently represent a hydrogen atom or a hydroxy, phenyl, pyridyl or substituted phenyl group; I represents an oxygen atom,

or a nitrogen atom;

J represents $-(CH_2)_n-$, $-CH=CH-$, $-OCH_2-$ or an oxygen atom; n represents an integral number in the range between 1 and 10, and m represents an integral number, 0, 1 or 2, or a pharmaceutically acceptable salt thereof;

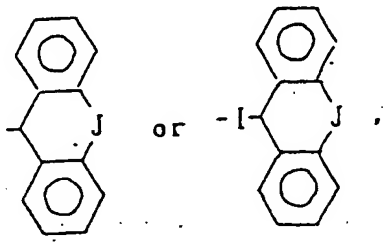
with the proviso that if C represents (a) or (b) then D does not represent (i) or (j) and I does not represent a nitrogen atom.

2. A compound according to claim 1 having the formula (II)

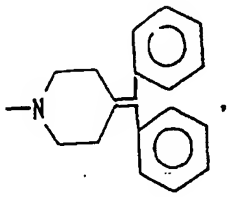


[II]

in which C' represents piperazine or piperidine, D' represents



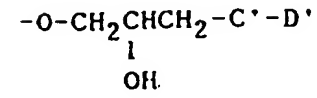
or C' and D' together form



and H, G, R^1, R^2, I and J are the same as those of the formula [I] or the pharmaceutically acceptable salt thereof.

3. The compound as set forth in claim 2, wherein, in formula [II], G represents a carbon atom, H represents a nitrogen atom, R^1 and R^2 are independently a hydrogen or halogen atom or a C_{1-4} alkyl group, J represents $-(CH_2)_2-$ or $-CH=CH-$, and I represents

4. The compound as set forth in claim 3, wherein, in the formula [II],

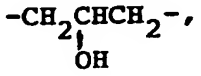


is at the 5-position of the condensed ring.

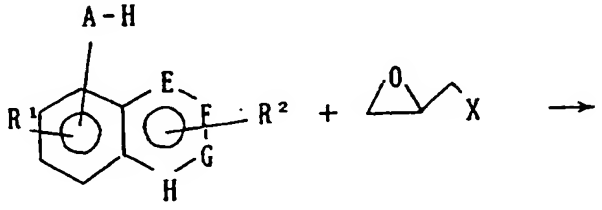
5. The compound as set forth in claim 4, wherein the compound of formula [II] is 5-[3-{4-(dibenzosuberane-5-yl) piperazine-1-yl}-2-hydroxypropoxy]quinoline.

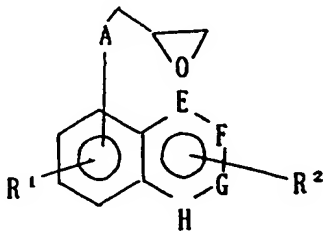
6. The compound as set forth in claim 4, wherein the compound of formula [II] is 5-[3-{4-diphenylmethylene) piperidine-1-yl}-2-hydroxypropoxyquinoline.

7. A process for the synthesis of a compound of the general formula [I] as set forth in claim 1, wherein B is

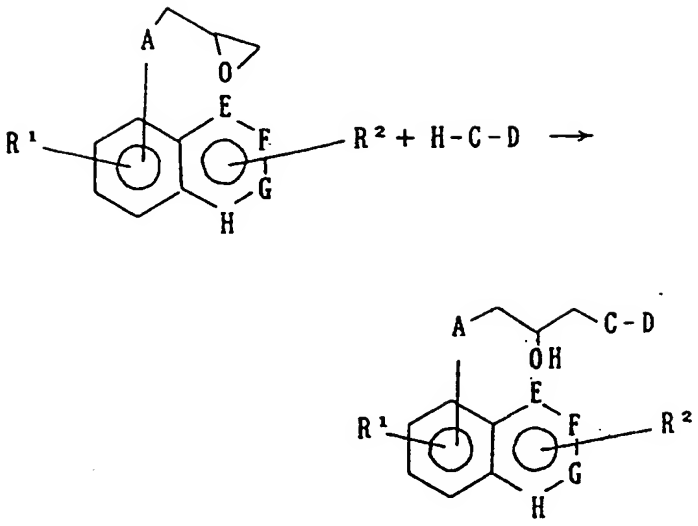


which comprises the steps of (a) reacting a heterocyclic compound represented by the following general formula with epihalogenohydrin in the presence of a base to form the corresponding epoxy compound



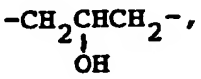


in which R^1, R^2, A, E, F, G and H are the same as those of the formula [I] and X represents a halogen atom,
and (b) thermally reacting the synthesized epoxy compound with a corresponding amine derivative, thereby obtaining the compound of the general formula [I].

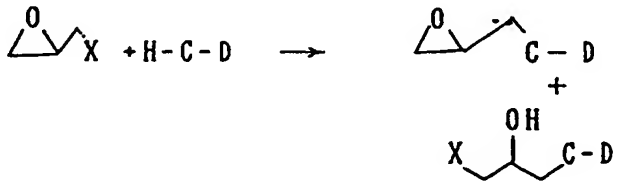


wherein R^1, R^2, A, E, F, G and H are as defined in claim 1.

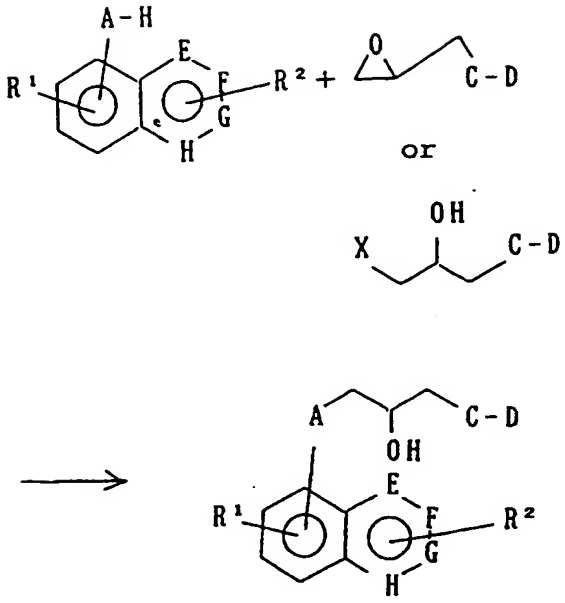
8. A process for the synthesis of a compound of the general formula [I] as set forth in claim 1, wherein B is



which comprises the steps of (a) reacting an epihalogenohydrin with a corresponding amine derivative thermally or in presence of a base in order to form the corresponding epoxy compound and hydroxyhalogen compound

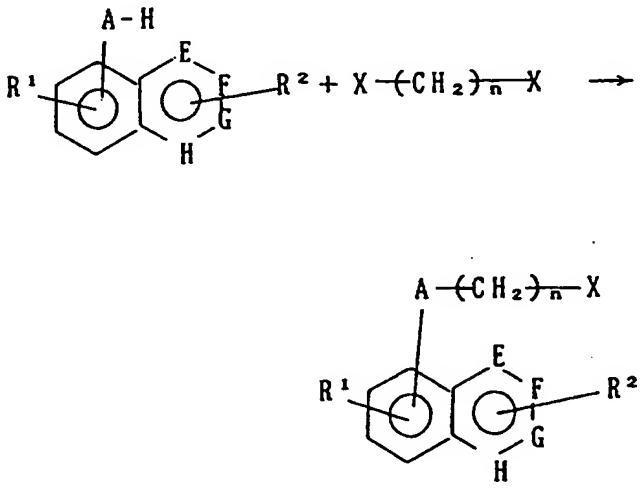


Wherein X is a halogen, and C and D are as defined in the formula [I], and (b) reacting a heterocyclic compound represented by the following formula with the above synthesized epoxy compound or hydroxyhalogen compound thermally or in the presence of a base or acid, thereby obtaining the compound of the general formula [I].

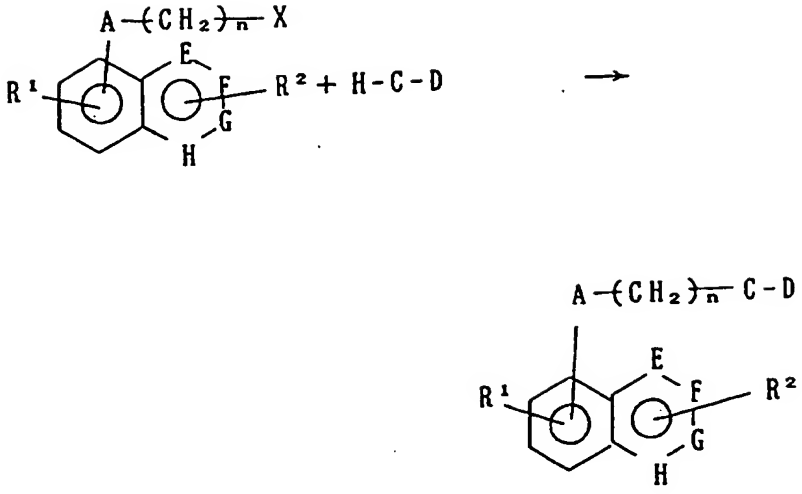


in which R^1, R^2, A, C, D, E, F, G and H are the same as those of the formula [I] and X represents a halogen atom.

9. A process for the synthesis of a compound of the general formula [I] wherein B is $-(CH_2)_n-$ as set forth in claim 1, which comprises the steps of (a) reacting a heterocyclic compound represented by the following general formula with a dihalogenoalkyl in the presence of a base to form the corresponding halogenoalkyl compound,

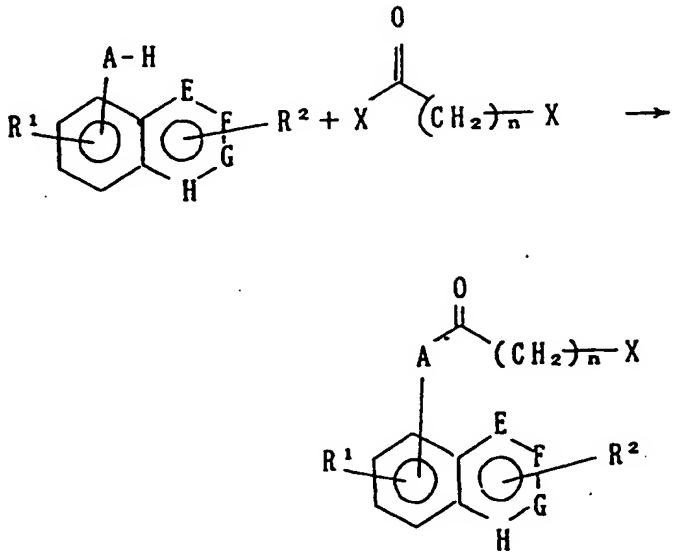


in which R^1, R^2, A, E, F, G, H and n are the same as those of formula [I] and X represents a halogen atom, and (b) thermally reacting the synthesized halogenoalkyl compound with a corresponding amine derivative, thereby obtaining the compound of the general formula [I].

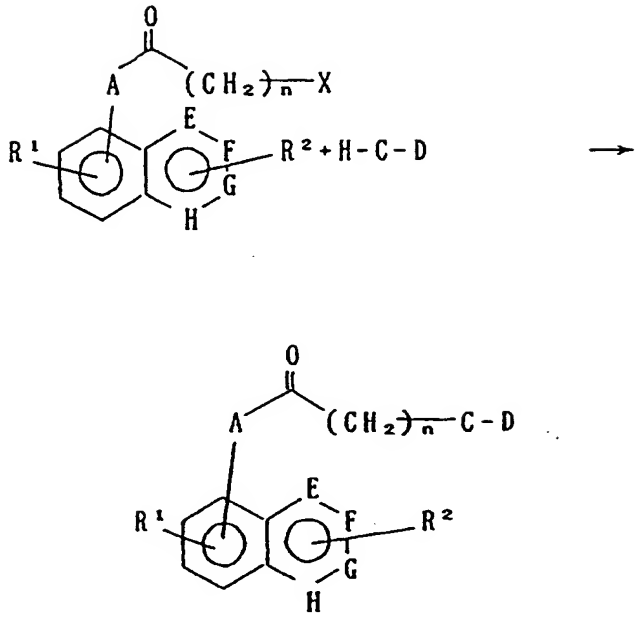


in which R^1, R^2, A, C, D, E, F, G, H and n are the same as those of formula [I] and X represents a halogen atom.

10. A process for the synthesis of a compound of the general formula [I] wherein B is $-CO(CH_2)_n-$ as set forth in claim 1, which comprises the steps of (a) reacting a heterocyclic compound represented by the following formula with an acid halide or an acid anhydride thermally or in the presence of a base in order to form the corresponding halide compound,



in which R^1, R^2, A, E, F, G, H and n are the same as those of the formula [I], and (b) thermally reacting the synthesized halide compound with a corresponding amine derivative, thereby obtaining the compound of the general formula [I].



in which R^1, R^2, A, C, D, E, F, G, H, n and X are the same as those of the formula [I].

11. The process as set forth in claim 7 for synthesis of a compound of the general formula [II], which comprises the steps of reacting a 5-hydroxyquinoline derivative with epichlorohydrin in a solvent in the presence of a base, removing the solvent after the reaction, extracting the residues with chloroform, and purifying the extract by silica gel column chromatography, thereby obtaining an epoxy compound, and steps of dissolving said epoxy compound and an amine derivative of the formula H-C'-D', wherein C' and D' are the same as those of the formula [II], in a solvent, heating the same under reflux to complete the reaction, and purifying the residues, after removing the solvent, by silica gel column chromatography, thereby obtaining the compound of the general formula [II].

12. A pharmaceutical composition for the potentiation of the effect of anticancer drugs, which comprises a compound of the general formula [I] as set forth in claim 1 together with a pharmaceutically acceptable carrier or diluent.

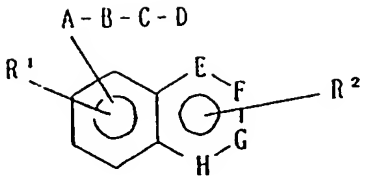
13. The pharmaceutical composition as set forth in claim 12, also containing a non-antimetabolic anticancer agent for simultaneous or sequential administration.

14. The pharmaceutical composition as set forth in claim 13, in which the non-antimetabolic anticancer agent is vincristine and/or adriamycin.

15. The pharmaceutical composition of claim 12, 13 or 14 which is: a peroral preparation in a form of tablet, granule, powder, suspension, capsule or syrup; injections; depositories; or isotonic fluids for infusion.

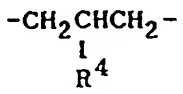
16. The compound as set forth in claim 4, wherein the compound of formula [II] is 5-[3-{4-dibenzosuberane-5-ylidene)piperidine-1-yl}-2-hydroxypropoxy]quinoline.

17. Use of a compound of the general formula [X] as defined below in preparing a composition for use in a method of treating cancer, which comprises potentiating the effect of an anticancer drug by administering to a patient in need of same an effective amount of an anticancer drug independently or in combination with the compound of the general formula [X]:

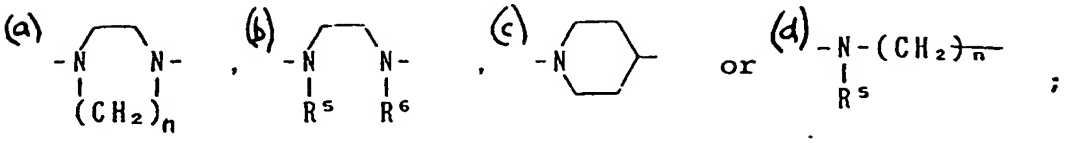


[X]

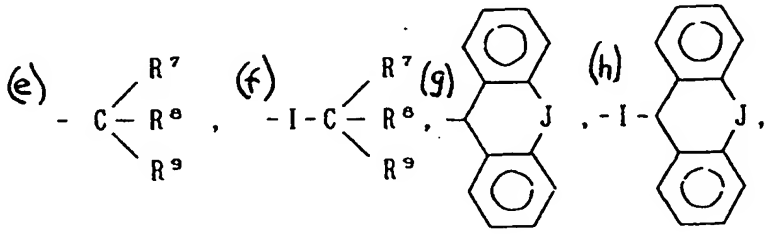
in which A represents an oxygen or sulfur atom or a methylene, amino or -NR^3 group, which is bound to any available position on the condensed benzene ring; B represents -$(CH_2)_n$-,

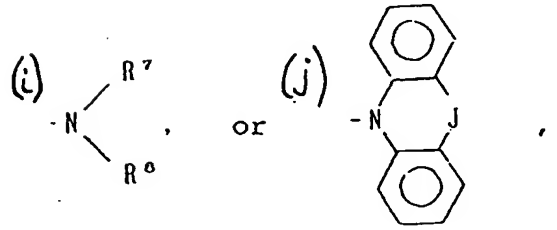


or -$CO(CH_2)_n$-; C represents

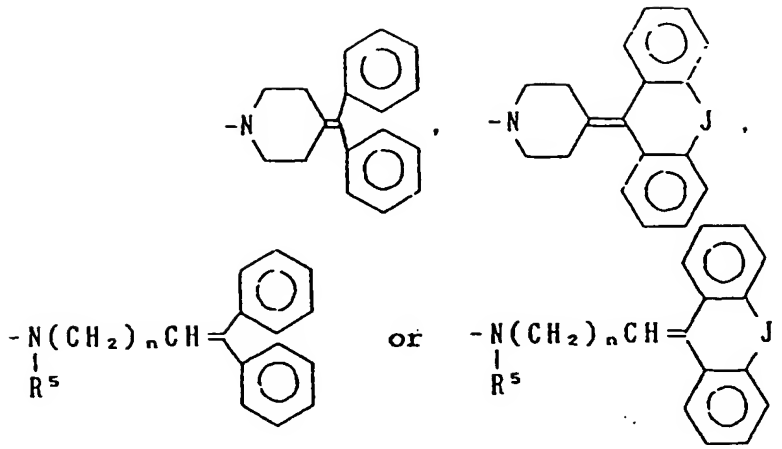


D represents





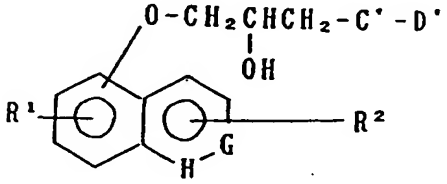
with the proviso that if C is (a) or (b) then D is not (i) or (j) and I is not a nitrogen atom; or C and D can together form



E, F, G and H each independently represent a carbon or nitrogen atom, provided that either one or two of them is nitrogen, R^1 and R^2 each independently represent a hydrogen or halogen atom, a C_{1-4} alkyl, amino group, substituted amino group, a C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylsulfonyl, trifluoromethyl, cyano, nitro, amide or hydroxy group, wherein R^1 and R^2 may be on any position available on the condensed ring or one each on each of the rings or both on the same ring of which the condensed ring is formed; R^3 represents a hydrogen atom or a C_{1-4} alkyl or acyl group; R^4 represents a hydroxyl, alkylamino (where alkyl is C_{1-4}), C_{1-4} alkoxyl or C_{1-2} acyloxy group; R^5 and R^6 each independently represent a hydrogen atom or a C_{1-4} alkyl or hydroxyalkyl group; R^7, R^8 and R^9 each independently represent a hydrogen atom or a hydroxy, phenyl, pyridyl or substituted phenyl group; I represents an oxygen atom, $-(CH_2)_n-$,

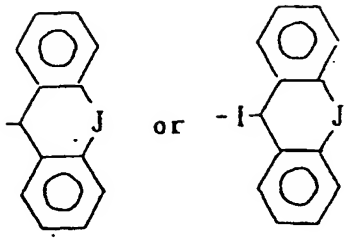
or a nitrogen atom;
J represents $-(CH_2)_n-$, $-CH=CH-$, $-OCH_2-$ or an oxygen atom; n represents an integral number in the range between 1 and 10, and m represents an integral number, 0, 1 or 2, or a pharmaceutically acceptable salt thereof.

18. Use according to claim 17 wherein the compound has the formula (XI)

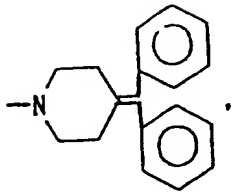


[XI]

in which C' represents piperazine or piperidine, D' represents



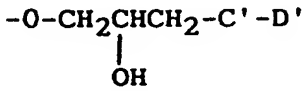
or C' and D' together form



and H, G, R^1, R^2, I and J are the same as those of the formula [X] or the pharmaceutically acceptable salt thereof.

19. Use as set forth in claim 18, wherein, in formula [XI], G represents a carbon atom, H represents a nitrogen atom, R^1 and R^2 are independently a hydrogen or halogen atom or a C_{1-4} alkyl group, J represents $-(CH_2)_2-$ or $-CH=CH-$, and
I represents

20. Use as set forth in claim 19 wherein, in the formula [XI],



is at the 5-

21. Use as set forth in claim 20, wherein the compound of formula [XI] is 5-[3-{4-(dibenzosuberane-5-yl) piperazine-1-yl}-2-hydroxypropoxy]quinoline.

22. Use as set forth in claim 20, wherein the compound of formula [XI] is 5-[3-{4-diphenylmethylene]-piperidine-1-yl}-2-hydroxypropoxyquinoline.

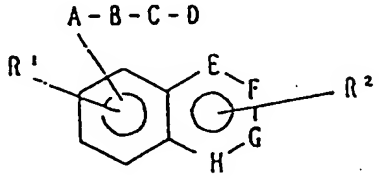
23. Use according to any of claims 17-22 in which the amount of the compound administered is in the range 1-1,000 mg a day in a single or divided dose.

24. The compound as set forth in claim 1, wherein the compound of formula [1] is 5-[3-{4(2,2-diphenylacetyl) piperazine-1-yl}-2-hydroxypropoxy]quinoline.

25. Use as set forth in claim 17, wherein the compound of formula [X] is 5-[3-{4-(2,2-diphenylacetyl) piperazine-1-yl}-2-hydroxypropoxy]quinoline.

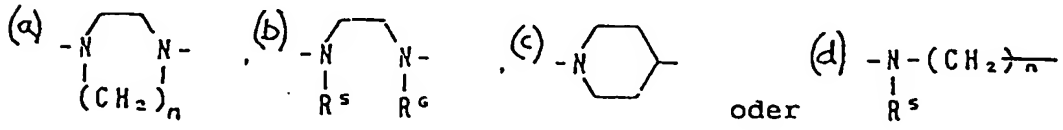
Patentansprüche

1. Verbindung der allgemeinen Formel (I)

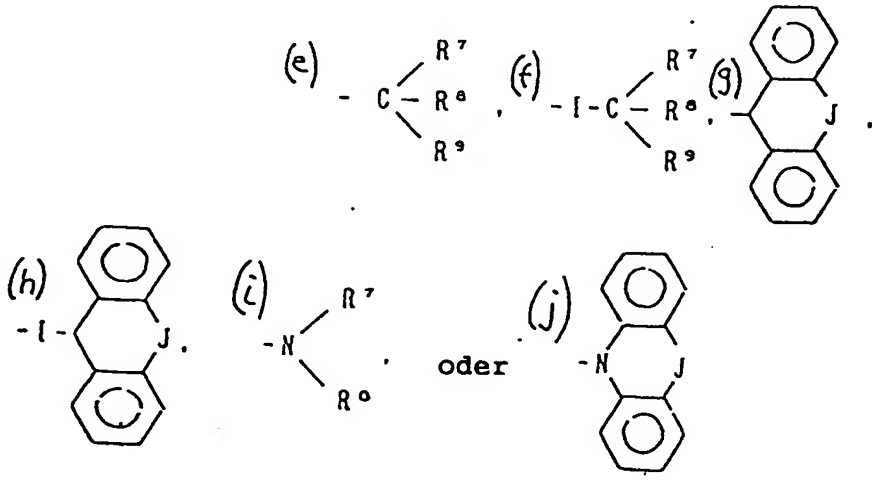


[I]

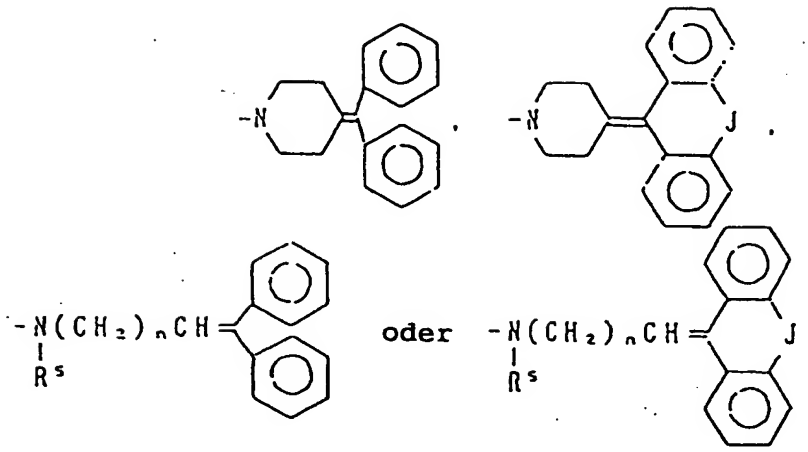
wobei A ein Sauerstoff- oder Schwefel-Atom oder eine Methylen-, eine Amino- oder eine -NR^3-Gruppe darstellt, die an eine verfügbare Position des kondensierten Benzolrings gebunden ist; wobei B -$(CH_2)_n$-, -$CH_2CHR^4CH_2$- oder -$CO(CH_2)_n$ darstellt; wobei C



darstellt; wobei D



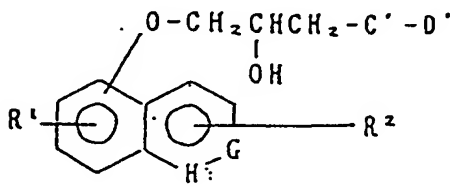
darstellt; oder wobei C und D gemeinsam



bilden können; wobei E, F, G und H jeweils unabhängig voneinander ein Kohlenstoff- oder Stickstoff-Atom darstellen, unter der Voraussetzung, daß entweder eines oder zwei von diesen Stickstoff ist; wobei R^1 und R^2 jeweils unabhängig voneinander ein Wasserstoff- oder ein Halogen-Atom, eine Alkyl-Gruppe mit 1 - 4 C-Atomen, eine Amino-Gruppe, eine substituierte Amino-Gruppe, eine Alkoxy-Gruppe mit 1 - 4 C-Atomen, eine Alkylthio-Gruppe mit 1 - 4 C-Atomen, eine Alkylsulfonyl-Gruppe mit 1 - 4 C-Atomen, eine Trifluormethyl-Gruppe, eine Cyano-Gruppe, eine Nitro-Gruppe, eine Amid-Gruppe oder eine Hydroxy-Gruppe darstellen, wobei R^1 und R^2 an jeglicher verfügbaren Position an dem kondensierten Ring sitzen können, oder wobei jeweils ein Rest an jeweils einem Ring sitzt, oder wobei beide Reste an demselben Ring sitzen, aus dem der kondensierte Ring gebildet wird; wobei R^3 ein Wasserstoff-Atom oder eine Alkyl- oder Acyl-Gruppe mit 1 - 4 C-Atomen darstellt; wobei R^4 eine Hydroxyl-Gruppe, eine kurzkettige Alkylamino-Gruppe mit einem Alkyl-Rest von 1 - 4 C-Atomen, eine Alkoxy-Gruppe mit 1 - 4 C-Atomen oder eine Acyloxy-Gruppe mit 1 - 2 C-Atomen darstellt; wobei R^5 und R^6 jeweils unabhängig voneinander ein Wasserstoff-Atom oder eine Alkyl- oder eine Hydroxyalkyl-Gruppe mit 1 - 4 C-Atomen darstellen; wobei R^7, R^8 und R^9 jeweils unabhängig voneinander ein Wasserstoff-Atom oder eine Hydroxy-Gruppe, eine Phenyl-, eine Pyridyl-Gruppe oder eine substituierte Phenyl-Gruppe darstellen; wobei I ein Sauerstoff-Atom,

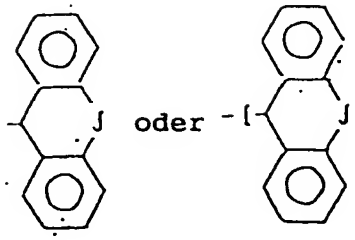
oder ein Stickstoff-Atom darstellt; wobei J $-(CH_2)_n-$, $-CH=CH-$, $-OCH_2-$ oder ein Sauerstoff-Atom darstellt; wobei n eine ganze Zahl im Bereich zwischen 1 und 10 darstellt, und wobei m eine ganze Zahl, nämlich 0, 1 oder 2, darstellt, oder ein pharmazeutisch verträgliches Salz, unter der Voraussetzung, daß D nicht (i) oder (j) darstellt und I kein Stickstoff-Atom darstellt, wenn C (a) oder (b) darstellt.

2. Die Verbindung nach Anspruch 1, die die Formel (II)

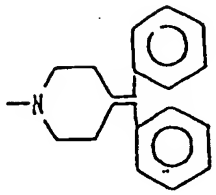


[[[]

hat, wobei C' Piperazin oder Piperidin darstellt, D'



oder C' und D' gemeinsam



bilden; und wobei H, G, R^1, R^2, I und J dieselben Gruppen sind wie bei Formel (I), oder ihr pharmazeutisch verträgliches Salz.

3. Die Verbindung nach Anspruch 2, wobei in Formel (II) G ein Kohlenstoff-Atom darstellt, H ein Stickstoff-Atom darstellt, R^1 und R^2 unabhängig voneinander ein Wasserstoff- oder ein Halogen-Atom oder eine Alkyl-Gruppe mit 1 - 4 C-Atomen darstellen, wobei J $-(CH_2)_2-$ oder $-CH=CH-$ darstellt; und wobei I

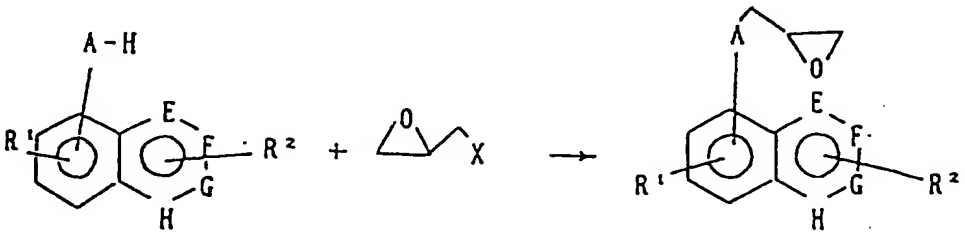
darstellt.

4. Die Verbindung nach Anspruch 3, wobei in Formel (II) $-O-CH_2-CHOH-CH_2-C'-D'$an der 5-Position des kondensierten Ringes sitzt.

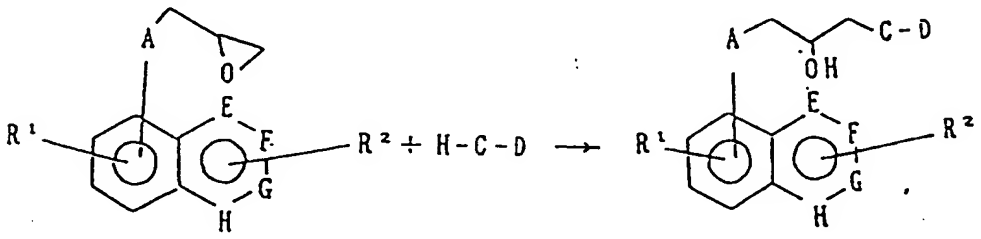
5. Die Verbindung nach Anspruch 4, wobei die Verbindung der Formel (II) 5-[3-{4-(Dibenzosuberan-5-yl)-piperazin-1-yl}-2-hydroxypropoxy]chinolin ist.

6. Die Verbindung nach Anspruch 4, wobei die Verbindung der Formel (II) 5-[3-{4-(Diphenylmethylen)-piperidin-1-yl}-2-hydroxypropoxy]chinolin ist.

7. Verfahren zur Herstellung einer Verbindung der allgemeinen Formel (I) nach Anspruch 1, wobei B $-CH_2CHOHCH_2-$ ist, wobei das Verfahren die folgenden Schritte umfaßt: (a) eine heterocyclische Verbindung, dargestellt durch die folgende allgemeine Formel, in Gegenwart einer Base unter Bildung der entsprechenden Epoxy-Verbindung mit Epihalogenhydrin umzusetzen

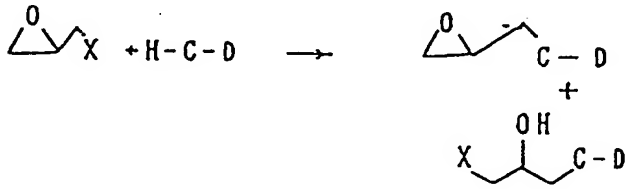


wobei R^1, R^2, A, E, F, G und H dieselben sind wie in Formel (I) und X ein Halogen-Atom darstellt, und (b) die synthetisierte Epoxy-Verbindung mit einem Derivat eines entsprechenden Amins umzusetzen, so daß die Verbindung der allgemeinen Formel (I) erhalten wird

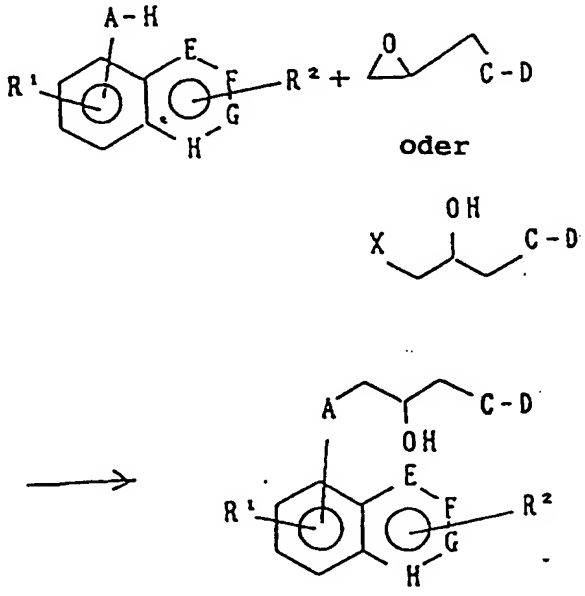


wobei R^1, R^2, A, E, F, G und H so sind, wie sie in Anspruch 1 definiert worden sind.

8. Verfahren zur Herstellung einer Verbindung der allgemeinen Formel (I) nach Anspruch 1, wobei B $-CH_2-CHOH-CH_2-$ ist, wobei das Verfahren die folgenden Schritte umfaßt:
(a) ein Epihalogenhydrin thermisch oder in Gegenwart einer Base mit einem Derivat eines entsprechenden Amins umzusetzen, so daß die entsprechende Epoxy- und Hydroxyhalogen-Verbindung gebildet wird

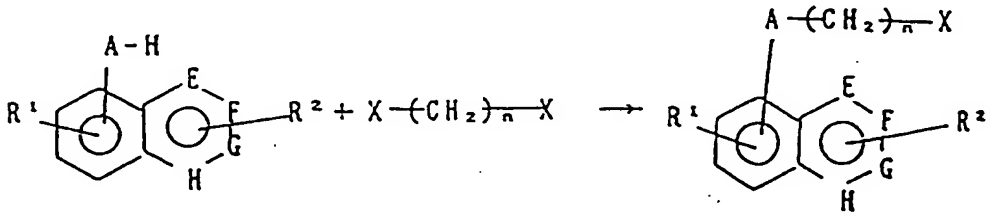


wobei X ein Halogen ist, und wobei C und D so sind, wie sie in Formel (I) definiert worden sind, und (b) eine heterocyclische Verbindung, dargestellt durch die folgende Formel, mit der oben hergestellten Epoxy- oder Hydroxyhalogen-Verbindung thermisch oder in Gegenwart einer Base oder Säure umzusetzen, so daß die Verbindung der allgemeinen Formel (I) erhalten wird

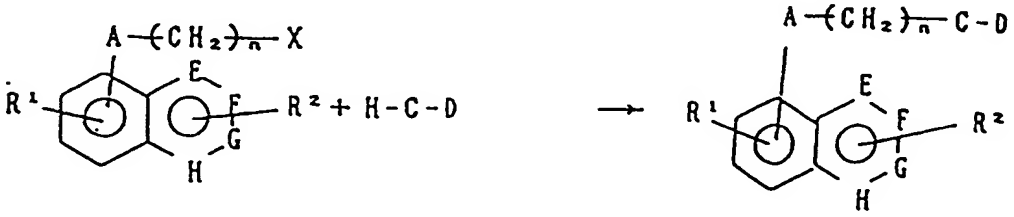


wobei R^1, R^2, A, C, D, E, F, G und H dieselben sind wie in Formel (I) und X ein Halogen-Atom darstellt.

9. Verfahren zur Herstellung einer Verbindung der allgemeinen Formel (I) nach Anspruch 1, wobei B $-(CH_2)_n-$ ist, wobei das Verfahren die folgenden Schritte umfaßt: (a) eine heterocyclische Verbindung, dargestellt durch die folgende allgemeine Formel, in Gegenwart einer Base unter Bildung der entsprechenden Halogenalkyl-Verbindung mit einer Dihalogenalkyl-Verbindung umzusetzen

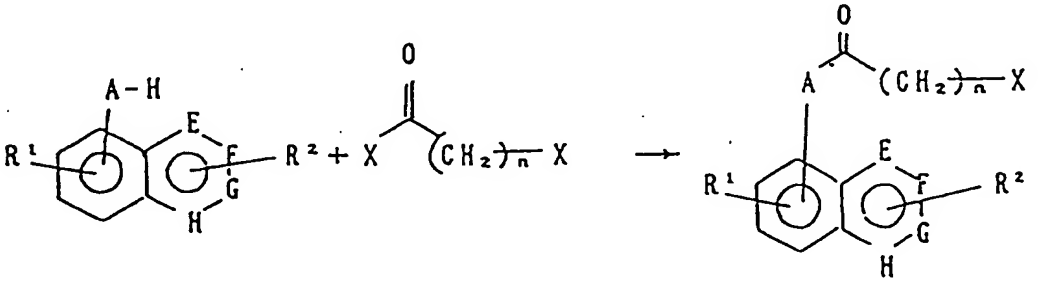


wobei R^1, R^2, A, E, F, G, H und n dieselben sind wie in Formel (I) und X ein Halogen-Atom darstellt, und (b) die synthetisierte Halogenalkyl-Verbindung mit einem Derivat eines entsprechenden Amins umzusetzen, so daß die Verbindung der allgemeinen Formel (I) erhalten wird

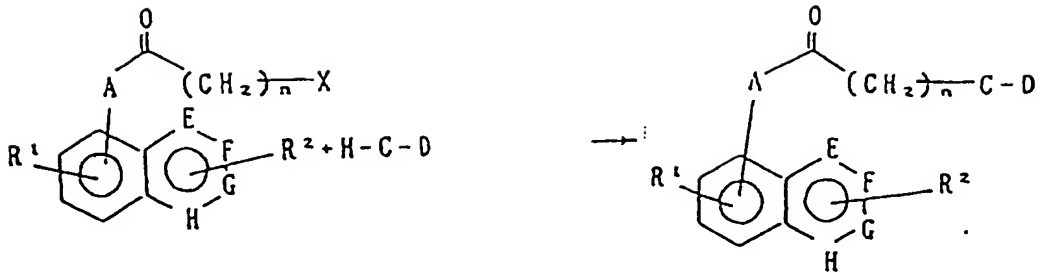


wobei R^1, R^2, A, C, D, E, F, G, H und n dieselben sind wie in Formel (I), und X ein Halogen-Atom darstellt.

10. Verfahren zur Herstellung einer Verbindung der allgemeinen Formel (I) nach Anspruch 1, wobei B $-CO-(CH_2)_n-$ ist, wobei das Verfahren die folgenden Schritte umfaßt: (a) eine heterocyclische Verbindung, dargestellt durch die folgende allgemeine Formel, thermisch oder in Gegenwart einer Base unter Bildung des entsprechenden Halogenids mit einem Säurehalogenid oder einem Säureanhydrid umzusetzen



wobei R^1, R^2, A, E, F, G, H und n dieselben sind wie in Formel (I), und (b) das synthetisierte Halogenid mit einem Derivat eines entsprechenden Amins umzusetzen, so daß die Verbindung der allgemeinen Formel (I) erhalten wird



wobei R^1, R^2, A, C, D, E, F, G, H, n und X dieselben sind wie in Formel (I) dargestellt.

11. Das Verfahren zur Herstellung einer Verbindung der allgemeinen Formel (II) nach Anspruch 7, wobei das Verfahren die Schritte umfaßt: ein Derivat des 5-Hydroxychinolins mit Epichlorhydrin in Gegenwart einer Base in einem Lösungsmittel umzusetzen, das Lösungsmittel nach der Reaktion zu entfernen, die Rückstände mit Chloroform zu extrahieren, und den Extrakt mittels Silikagel-Säulenchromatographie zu reinigen, so daß eine Epoxy-Verbindung erhalten wird, diese Epoxy-Verbindung und ein Derivat eines Amins der Formel H-C'-D', wobei C' und D' dieselben sind wie in der Formel (II), in einem Lösungsmittel zu lösen, diese unter Rückfluß zu erhitzen, um die Reaktion zu vervollständigen, und die Rückstände zu reinigen, nachdem das Lösungsmittel mittels Silikagel-Säulenchromatographie entfernt worden ist, so daß die Verbindung der allgemeinen Formel (II) erhalten wird.

12. Pharmazeutische Zusammensetzung zur Verstärkung der Wirkung von Antikrebs-Mitteln, die eine Verbindung der allgemeinen Formel (I) nach Anspruch 1 zusammen mit einem pharmazeutisch verträglichen Träger oder Verdünner umfaßt.

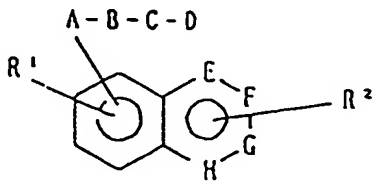
13. Die pharmazeutische Zusammensetzung nach Anspruch 12, die außerdem ein nicht-antimetabolisches Antikrebs-Mittel für die gleichzeitige oder sequentielle Verabreichung enthält.

14. Die pharmazeutische Zusammensetzung nach Anspruch 13, wobei das nicht- antimetabolische Antikrebs-Mittel Vincristin und/oder Adriamycin ist.

15. Die pharmazeutische Zusammensetzung nach Anspruch 12, 13 oder 14, die die folgende ist: eine perorale Zubereitung in Form einer Tablette, eines Granulats, eines Pulvers, einer Suspension, einer Kapsel oder eines Sirups; Injektionen; Depositorien; oder isotonische Lösungen für die Infusion.

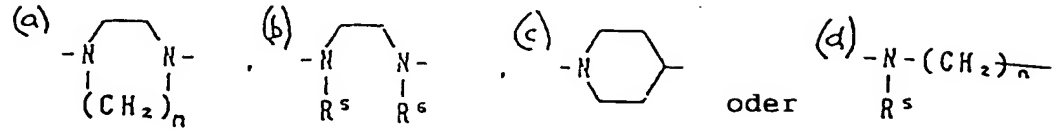
16. Die Verbindung nach Anspruch 4, wobei die Verbindung der Formel (II) 5-[3-{4-(Dibenzosuberan-5-yliden)piperidin-1-yl}-2-hydroxypropoxy]chinolin ist.

17. Verwendung einer Verbindung der allgemeinen Formel (X) wie unten definiert zur Herstellung einer Zusammensetzung für die Verwendung bei einem Verfahren zur Behandlung von Krebs, wobei die Behandlung umfaßt: die Wirkung eines Antikrebs-Mittels durch Verabreichung einer wirksamen Menge eines Antikrebs-Mittels unabhängig oder in Verbindung mit der Verbindung der allgemeinen Formel (X) an einen Patienten zu verstärken

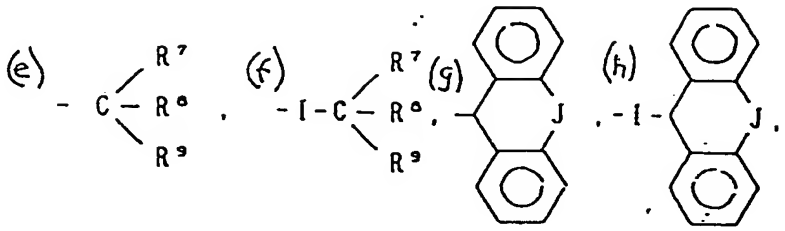


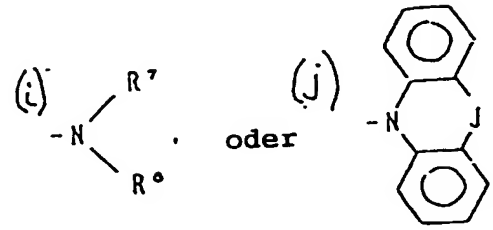
wobei A ein Sauerstoff- oder Schwefel-Atom oder eine Methylen-, eine Amino- oder eine $-NR^3$-Gruppe darstellt, die an eine verfügbare Position des kondensierten Benzolrings gebunden ist; wobei B $-(CH_2)_n-$

, $-CH_2-CHR^4-CH_2-$ oder $-CO-(CH_2)_n$ darstellt; wobei C

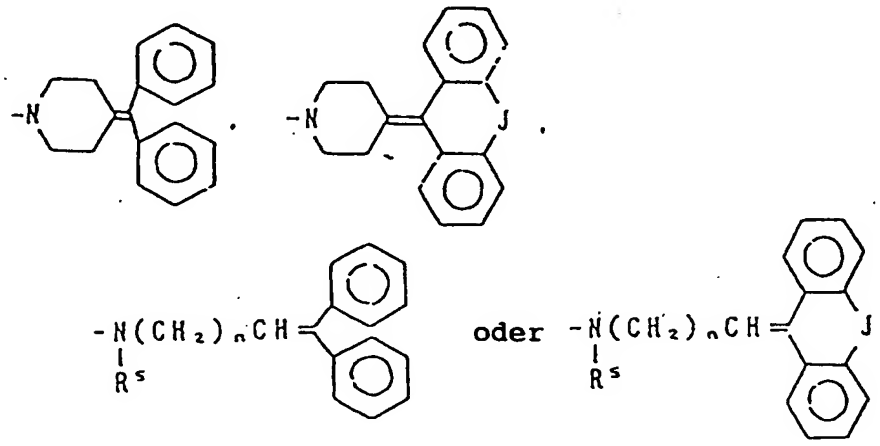


darstellt; wobei D





darstellt; unter der Voraussetzung, daß D nicht (i) oder (j) darstellt und I kein Stickstoff-Atom darstellt, wenn C (a) oder (b) darstellt; oder wobei C und D gemeinsam

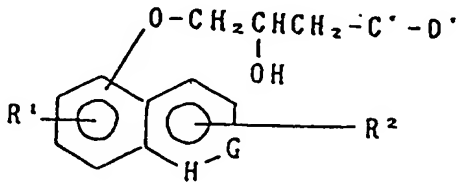


bilden können; wobei E, F, G und H jeweils unabhängig voneinander ein Kohlenstoff- oder Stickstoff-Atom darstellen, unter der Voraussetzung, daß entweder eines oder zwei von diesen Stickstoff ist; wobei R^1 und R^2 jeweils unabhängig voneinander ein Wasserstoff- oder ein Halogen-Atom, eine Alkyl-Gruppe mit 1 - 4 C-Atomen, eine Amino-Gruppe, eine substituierte Amino-Gruppe, eine Alkoxy-Gruppe mit 1 - 4 C-Atomen, eine Alkylthio-Gruppe mit 1 - 4 C-Atomen, eine Alkylsulfonyl-Gruppe mit 1 - 4 C-Atomen, eine Trifluormethyl-Gruppe, eine Cyano-Gruppe, eine Nitro-Gruppe, eine Amid-Gruppe oder eine Hydroxy-Gruppe darstellen, wobei R^1 und R^2 an jeglicher verfügbaren Position an dem kondensier-

ten Ring sitzen können, oder wobei jeweils ein Rest an jeweils einem Ring sitzt, oder wobei beide Reste an demselben Ring sitzen, aus dem der kondensierte Ring gebildet wird; wobei R^3 ein Wasserstoff-Atom oder eine Alkyl- oder Acyl-Gruppe mit 1 - 4 C-Atomen darstellt; wobei R^4 eine Hydroxyl-Gruppe, eine kurzkettige Alkylamino-Gruppe mit einem Alkyl-Rest von 1 - 4 C-Atomen, eine Alkoxy-Gruppe mit 1 - 4 C-Atomen oder eine Acyloxy-Gruppe mit 1 - 2 C-Atomen darstellt; wobei R^5 und R^6 jeweils unabhängig voneinander ein Wasserstoff-Atom oder eine Alkyl- oder eine Hydroxyalkyl-Gruppe mit 1 - 4 C-Atomen darstellen; wobei R^7, R^8 und R^9 jeweils unabhängig voneinander ein Wasserstoff-Atom oder eine Hydroxy-Gruppe, eine Phenyl-, eine Pyridyl-Gruppe oder eine substituierte Phenyl-Gruppe darstellen; wobei I ein Sauerstoff-Atom,

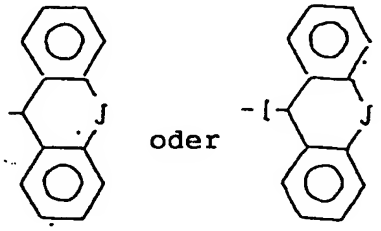
oder ein Stickstoff-Atom darstellt; wobei J $-(CH_2)_n-$, $-CH=CH-$, $-OCH_2-$ oder ein Sauerstoff-Atom darstellt; wobei n eine ganze Zahl im Bereich zwischen 1 und 10 darstellt, und wobei m eine ganze Zahl, nämlich 0, 1 oder 2, darstellt, oder eines ihrer pharmazeutisch verträglichen Salze.

18. Die Verweundung nach Anspruch 17, wobei die Verbindung die Formel (XI)

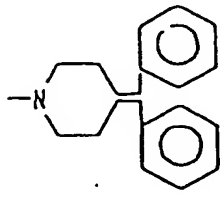


[XI]

hat, wobei C' Piperazin oder Piperidin darstellt, wobei D'



oder wobei C' und D' gemeinsam



bilden; und wobei H, G, R^1, R^2, I und J dieselben sind wie für die Formel (X), oder ihr pharmazeutisch verträgliches Salz.

19. Die Verwendung nach Anspruch 18, wobei in Formel (XI) G ein Kohlenstoff-Atom darstellt, H ein Stickstoff-Atom darstellt, R^1 und R^2 unabhängig voneinander ein Wasserstoff- oder ein Halogen-Atom oder eine Alkyl-Gruppe mit 1 - 4 C-Atomen darstellen, wobei J $-(CH_2)_2-$ oder $-CH=CH-$ darstellt; und wobei I

darstellt.

20. Die Verwendung nach Anspruch 19, wobei in der Formel (XI) -O-CH_2-CHOH-CH_2-C'-D' an der 5-Position des kondensierten Ringes sitzt.

21. Die Verwendung nach Anspruch 20, wobei die Verbindung der Formel (XI) 5-[3-{4-(Dibenzosuberan-5-yl)piperazin-1-yl}-2-hydroxypropoxy]chinolin ist.

22. Die Verwendung nach Anspruch 20, wobei die Verbindung der Formel (XI) 5-[3-{4-(Diphenylmethylen)-piperidin-1-yl}-2-hydroxypropoxy]chinolin ist.

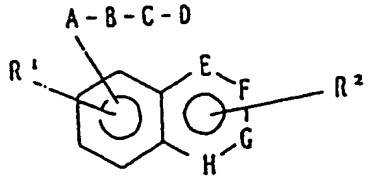
23. Die Verwendung nach einem der Ansprüche 17 - 22, wobei die Menge der verabreichten Verbindung in dem Bereich von 1 - 1.000 mg pro Tag in einer einzigen oder mehreren Dosen liegt.

24. Die Verbindung nach Anspruch 1, wobei die Verbindung der Formel (I) 5-[3-{4-(2,2-Diphenylacetyl)-piperazin-1-yl}-2-hydroxypropoxy]chinolin ist.

25. Die Verwendung nach Anspruch 17, wobei die Verbindung der Formel (X) 5-[3-{4-(2,2-Diphenylacetyl)-piperazin-1-yl}-2-hydroxypropoxy]chinolin ist.

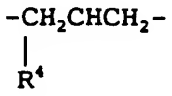
Revendications

1. Composé de formule générale [I]

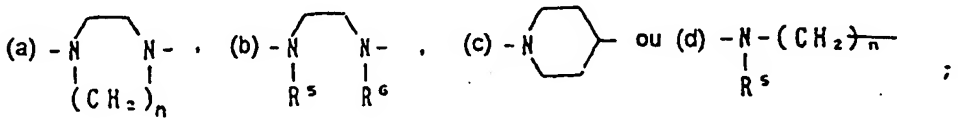


[I]

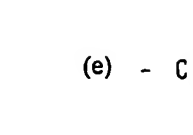
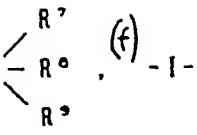
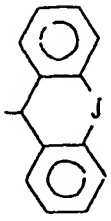
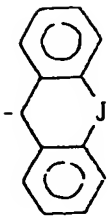
dans laquelle A représente un atome d'oxygène ou de soufre ou un groupe méthylène, amino ou -NR^3, qui est relié à une position quelconque disponible sur le noyau benzénique condensé; B représente -$(CH_2)_n$-,

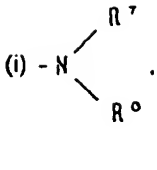
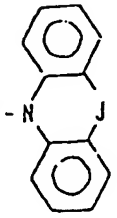


ou -$CO(CH_2)_n$-; C représente

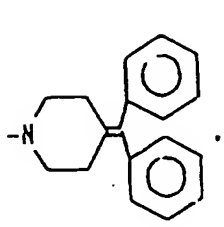
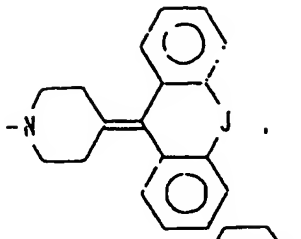


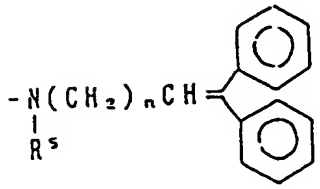
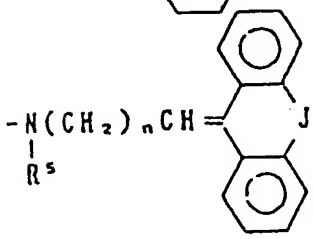
D représente

(e)  (f)  (g)  (h) 

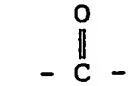
 ou (j) 

C et D peuvent former ensemble

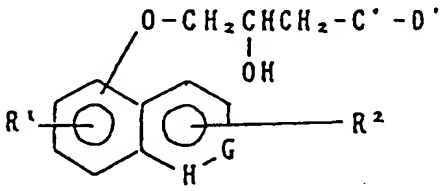
 ou 

E, F, G et H représentent chacun indépendamment un atome de carbone ou d'azote, à condition que soit un soit deux d'entre eux soit un atome d'azote, R^1 et R^2 représentent chacun indépendamment un atome d'hydrogène ou d'halogène, un groupe alkyle en C_1 à C_4, un groupe amino, un groupe amino substitué, un groupe alcoxy en C_1 à C_4, un groupe alkylthio en C_1 à C_4, alkylsulfonyle en C_1 à C_4, trifluorométhyle, cyano, nitro, amide ou hydroxy, dans lesquels R^1 et R^2 peuvent être sur une position quelconque disponible sur le noyau condensé ou un de chaque sur chacun des noyaux ou les deux sur le même noyau dont est formé le noyau condensé; R^3 représente un atome d'hydrogène ou un groupe alkyle(en C_1 à C_4) ou acyle; R^4 représente un groupe hydroxyle, alkylamino inférieure (où l'alkyle est en C_1 à C_4), un groupe alkoxyle en C_1 à C_4 ou acyloxy en C_1 à C_2; R^5 et R^6 représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle ou hydroxyalkyle en C_1 à C_4 ; R^7, R^8 et R^9 représentent chacun indépendamment un atome d'hydrogène ou un groupe hydroxy, phényle, pyridyle ou phényle substitué; I représente un radical oxygène,



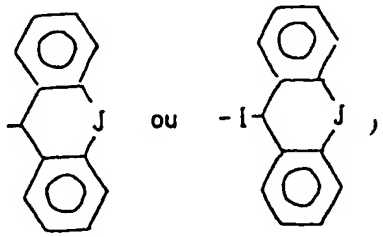
ou azote; J représente $-(CH_2)_n-$, $-CH=CH-$, $-OCH_2-$ ou un atome d'oxygène; n représente un nombre entier dans la gamme comprise entre 1 et 10, et m représente un nombre entier, 0, 1 ou 2, ou un sel pharmaceutiquement acceptable de celui-ci; à condition que si C représente (a) ou (b) alors D ne représente pas (i) ou (j) et I ne représente pas un atome d'azote.

2. Composé selon la revendication 1 ayant la formule (II)

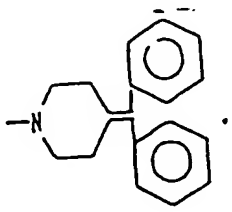


[[[]

dans laquelle C' représente un groupe pipérazine ou pipéridine, D' représente

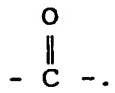


ou C' et D' forment ensemble

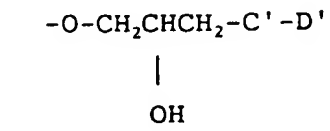


et H, G, R^1, R^2, I et J sont identiques à ceux de la formule [I] ou un sel pharmaceutiquement acceptable de celui-ci.

3. Composé selon la revendication 2, dans lequel, dans la formule [II], G représente un atome de carbone, H représente un atome d'azote, R^1 et R^2 représentent indépendamment un atome d'hydrogène ou d'halogène ou un groupe alkyle en C_1 à C_4, J représente $-(CH_2)_2-$ ou $-CH=CH-$, et I représente



4. Composé selon la revendication 3, dans lequel, dans la formule (II],

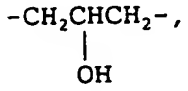


est à la position 5 du noyau condensé.

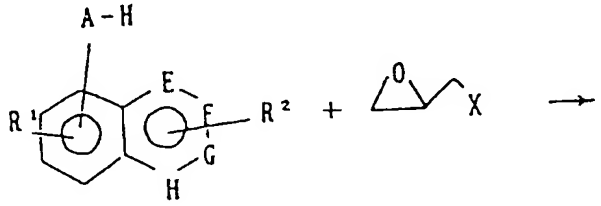
5. Composé selon la revendication 4, dans lequel le composé de formule [II] est la 5-[3-{4-(dibenzosubérane-5-yl)pipérazine-1-yl}-2-hydroxypropoxy]quinoléine.

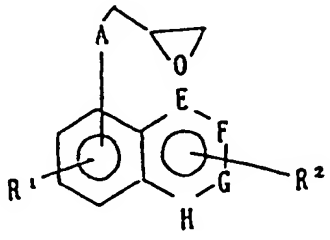
6. Composé selon la revendication 4, dans lequel le composé de formule [II] est la 5-[3-{4-(diphénylméthylène)pipéridine-1-yl}-2-hydroxypropoxy]quinoléine

7. Procédé pour la synthèse d'un composé de formule générale [I] comme exposé dans la revendication 1, dans laquelle B est

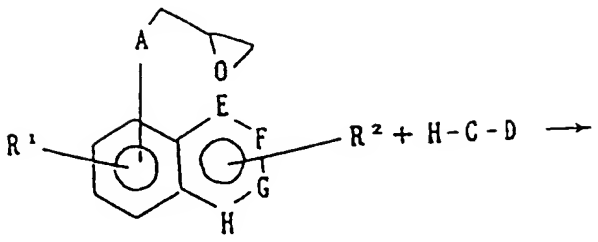


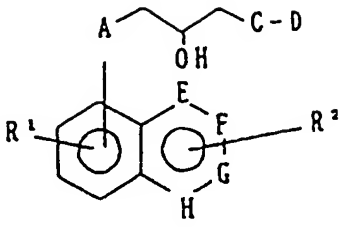
qui comprend les étapes consistant (a) à faire réagir un composé hétérocyclique représenté par la formule générale suivante avec une épihalogénohydrine en présence d'une base afin de former le composé époxy correspondant





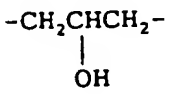
dans laquelle R^1, R^2, A, E, F, G et H sont identiques à ceux de formule [I] et X représente un atome d'halogène,
et (b) à faire réagir thermiquement le composé époxy synthétisé avec un dérivé amine correspondant, obtenant ainsi le composé de formule générale [I],



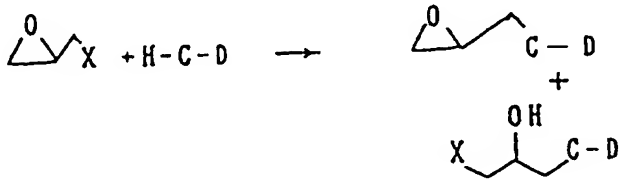


dans laquelle R^1, R^2, A, E, F, G et H sont tels que définis dans la revendication 1.

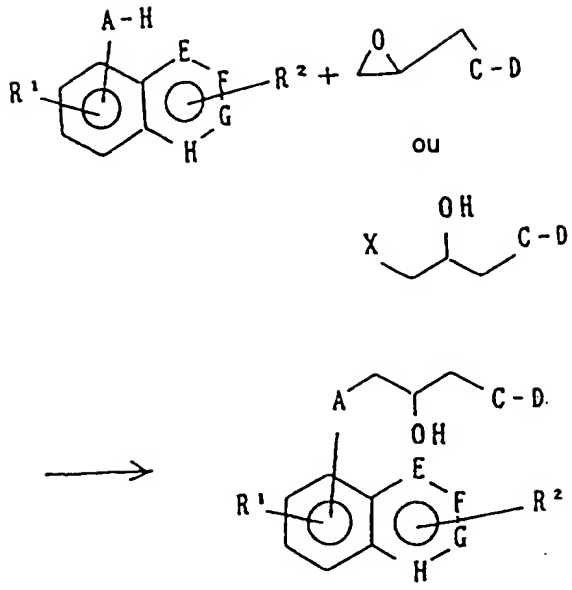
8. Procédé pour la synthèse d'un composé de formule générale [I] comme exposé dans la revendication 1, dans laquelle B est



qui comprend les étapes consistant (a) à faire réagir une épihalogénohydrine avec un dérivé amine correspondant thermiquement ou en présence d'une base afin de former le composé époxy correspondant et un composé hydroxyhalogéné

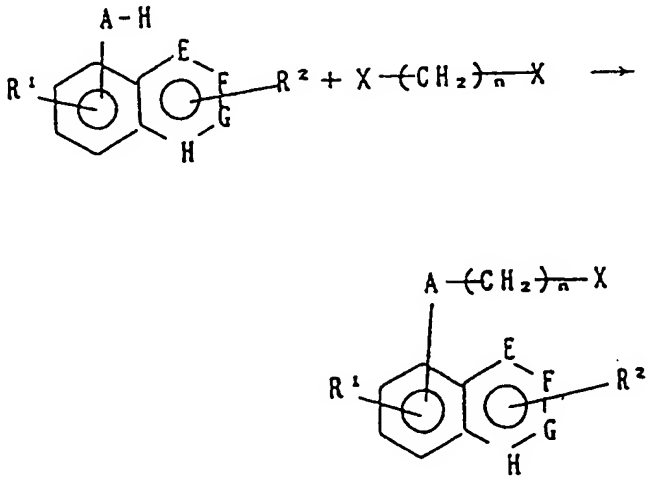


dans lesquelles X est un atome d'halogène, et C et D sont tels que définis dans la formule [I], et (b) à faire réagir un composé hétérocyclique représenté par la formule suivante avec le composé époxy synthétisé ci-dessus ou le composé hydroxyhalogéné thermiquement ou en présence d'une base ou d'un acide, obtenant ainsi le composé de formule générale [I].

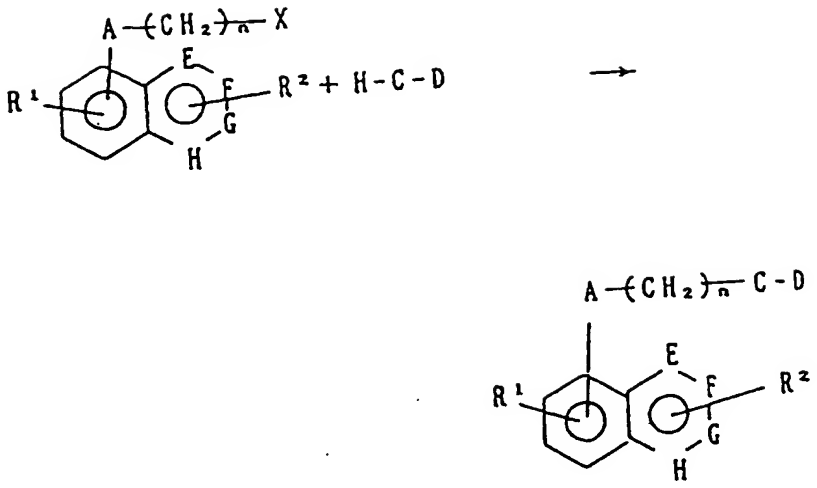


dans laquelle R^1, R^2, A, C, D, E, F, G et H sont identiques à ceux de la formule [I] et X représente un atome d'halogène.

9. Procédé pour la synthèse d'un composé de formule générale [I] dans laquelle B est $-(CH_2)_n-$ selon la revendication 1, qui comprend les étapes consistant (a) à faire réagir un composé hétérocyclique représenté par la formule générale suivante avec un dihalogénoalkyle en présence d'une base afin de former le composé halogénoalkyle correspondant

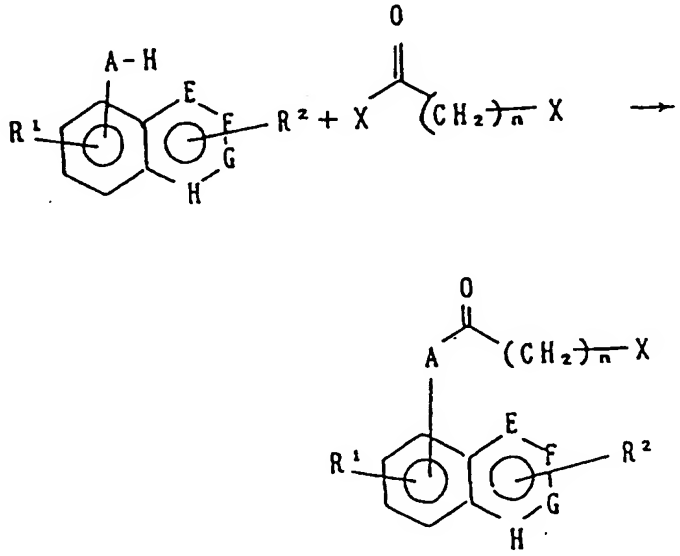


dans laquelle R^1, R^2, A, E, F, G H et n sont identiques à ceux de formule [I] et X représente un atome d'halogène, et (b) à faire réagir thermiquement le composé halogénoalkyle synthétisé avec un dérivé amine correspondant, obtenant ainsi le composé de formule générale [I]

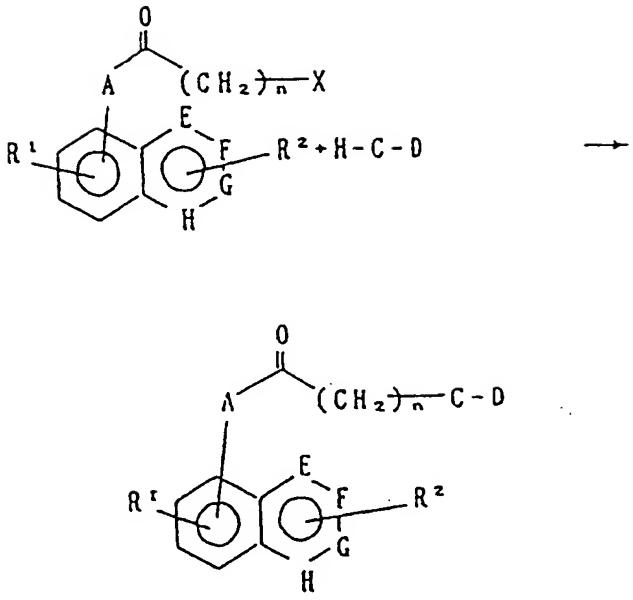


dans laquelle R^1, R^2, A, C, D, E, F, G, H et n sont identiques à ceux de formule [I] et X représente un atome d'halogène.

10. Procédé pour la synthèse d'un composé de formule générale [I], dans lequel B est $-CO(CH_2)_n-$ comme exposé dans la revendication 1, qui comprend les étapes consistant (a) à faire réagir un composé hétérocyclique représenté par la formule suivante avec un halogénure d'acide ou un anhydride thermiquement ou en présence d'une base afin de former le composé halogénure correspondant,



dans lequel R^1, R^2, A, E, F, G et H et n sont identiques à ceux de formule [I], et (b) à faire réagir thermiquement le composé halogénure synthétisé avec un dérivé amine correspondant, obtenant ainsi le composé de la formule générale [I],



dans laquelle R^1, R^2, A, C, D, E, F, G, H, n et X sont identiques à ceux de la formule [I].

11. Procédé selon la revendication 7 pour la synthèse d'un composé de formule générale [II], qui comprend les étapes consistant à faire réagir un dérivé de 5-hydroxyquinoléine avec l'épichorhydrine dans un solvant en présence d'une base, à éliminer le solvant après la réaction, a extraire les résidus avec du chloroforme, et à purifier l'extrait par chromatographie en colonne sur gel de silice, obtenant ainsi un composé époxy, et les étapes consistant à dissoudre ledit composé époxy et un dérivé amine de formule H-C'-D', dans laquelle C' et D' sont identiques à ceux de formule [II], dans un solvant, à chauffer à reflux pour achever la réaction, et à purifier les résidus, ensuite à éliminer le solvant, par chromatographie en colonne sur gel de silice, obtenant ainsi le composé de formule générale [II].

12. Composition pharmaceutique pour la potentialisation de l'effet de médicaments anti-cancéreux, qui comprend un composé de la formule générale [I] selon la revendication 1 conjointement avec un véhicule ou un diluant pharmaceutiquement acceptable.

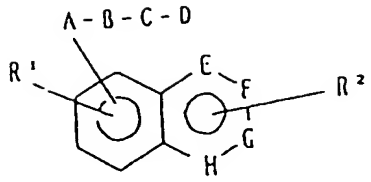
13. Composition pharmaceutique selon la revendication 12, contenant également un agent anti-cancéreux non anti-métabolique pour une administration simultanée ou séquentielle.

14. Composition pharmaceutique selon la revendication 13, dans laquelle l'agent anti-cancéreux non anti-métabolique est la vincristine et/ou l'adriamycine.

15. Composition pharmaceutique selon la revendication 12, 13 ou 14 qui est: une préparation perorale sous forme de comprimé, granulé, poudre, suspension, gélule ou sirop; d'injections; de suppositoires; ou de fluides isotoniques pour perfusion.

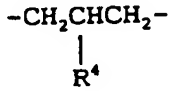
16. Composition selon la revendication 4, dans laquelle le composé de formule [II] est la 5-[3-{4-dibenzosubérane-5-ylidène)pipéridine-1-yl}-2-hydroxypropoxy]quinoléine.

17. Utilisation d'un composé de formule générale [X] comme défini ci-dessous dans la préparation d'une composition pour une utilisation dans un procédé de traitement du cancer, qui comprend la potentialisation de l'effet d'un médicament anti-cancéreux par l'administration à un patient ayant besoin de celui-ci d'une quantité efficace d'un médicament anti-cancéreux indépendamment ou en combinaison avec le composé de la formule générale [X]:

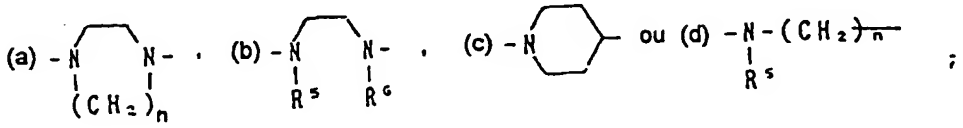


[X]

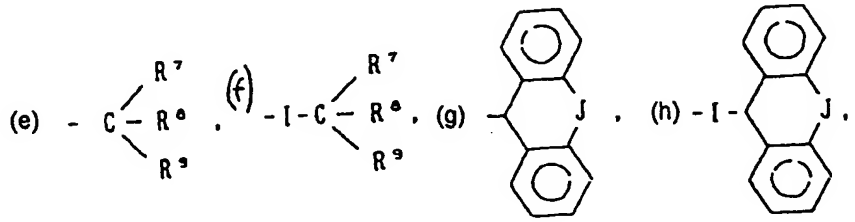
dans laquelle A représente un atome d'oxygène ou de soufre ou un groupe méthylène, amino ou -NR^3, qui est lié à une position quelconque disponible sur le noyau benzénique condensé; B représente -$(CH_2)_n$-,

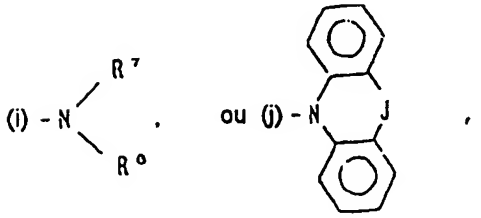


ou -$CO(CH_2)_n$-; C représente

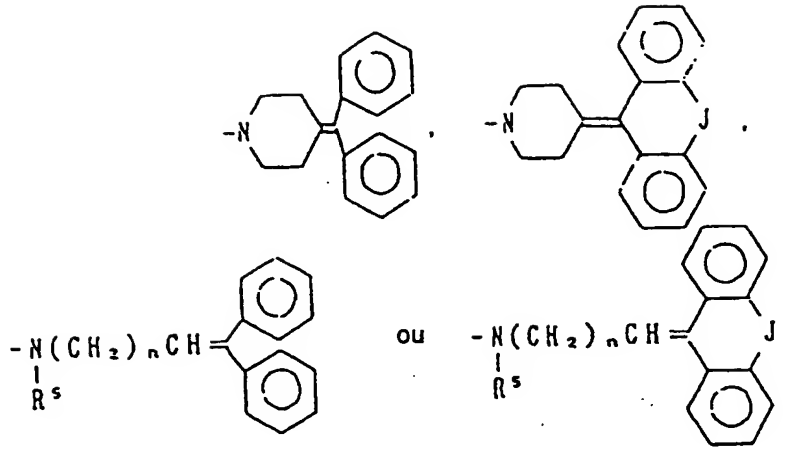


D représente





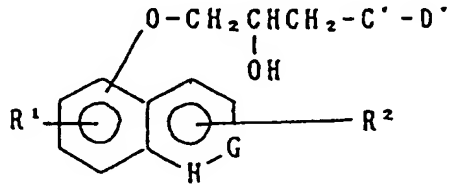
à condition que si C est (a) ou (b), alors D n'est pas (i) ou (j) et I n'est pas un atome d'azote; ou bien C et D peuvent former ensemble



E, F, G et H représentent chacun indépendamment un atome de carbone ou d'azote, à condition que soit un soit deux d'entre eux soit un atome d'azote, R^1 et R^2 représentent chacun indépendamment un atome d'hydrogène ou d'halogène, un groupe alkyle en C_1 à C_4, un groupe amino, un groupe amino substitué, un groupe alcoxy en C_1 à C_4, alkylthio en C_1 à C_4, alkylsulfonyle en C_1 à C_4, trifluorométhyle cyano, nitro, amide ou hydroxy, dans laquelle R^1 et R^2 peuvent être sur une position quelconque disponible sur le noyau condensé ou un de chaque sur chacun des noyaux ou les deux sur le même noyau dont est formé le noyau condensé; R^3 représente un atome d'hydrogène ou un groupe alkyle(en C_1 à C_4) ou un groupe acyle; R^4 représente un groupe hydroxyle, un groupe alkylamino inférieure (où l'alkyle est en C_1 à C_4), un groupe alkoxyle en C_1 à C_4 ou acyloxy en C_1 à C_2; R^5 et R^6 représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle ou hydroxyalkyle en C_1 à C_4; R^7, R^8 et R^9 représentent chacun indépendamment un atome d'hydrogène ou un groupe hydroxy, phényle, pyridyle ou phényle substitué; I représente un atome d'oxygène, $-(CH_2)_n-$

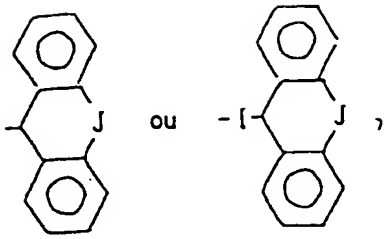
ou un atome d'azote; J représente $-(CH_2)_n-$, $-CH=CH-$, $-OCH_2-$ ou un atome d'oxygène; n représente un nombre entier dans la gamme comprise entre 1 et 10, et m représente un nombre entier, 0, 1 ou 2, ou un sel pharmaceutiquement acceptable de celui-ci.

18. Utilisation selon la revendication 17, dans laquelle le composé a la formule (XI)

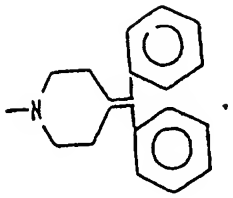


[XI]

dans laquelle C' représente un groupe pipérazine ou pipéridine, D' représente

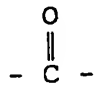


ou C' et D' forment ensemble

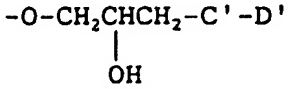


et H, G, R^1, R^2, I et J sont identiques à ceux de formule [X] ou un sel pharmaceutiquement acceptable de celui-ci.

19. Utilisation selon la revendication 18, dans laquelle, dans la formule [XI], G représente un atome de carbone, H représente un atome d'azote, R^1 et R^2 représentent indépendamment un atome d'hydrogène ou d'halogène ou un groupe alkyle en C_1 à C_4, J représente $-(CH_2)_2-$ ou -CH=CH-, et I représente



20. Utilisation selon la revendication 19, dans laquelle, dans la formule [I],



est à la position 5

21. Utilisation selon la revendication 20, dans laquelle le composé de formule [XI] est la 5-[3-{4-(dibenzosubérane-5-yl)pipérazine-1-yl}-2-hydroxypropoxy]quinoléine.

22. Utilisation selon la revendication 20, dans laquelle le composé de formule [XI] est la 5-[3-{4-(diphénylméthylène)pipéridine-1-yl}-2-hydroxypropoxy]quinoléine.

23. Utilisation selon l'une quelconque des revendications 17 à 22 dans laquelle la quantité du composé administré est dans la gamme de 1 à 1000 mg par jour en dose unique ou divisée.

24. Composé selon la revendication 1, dans lequel le composé selon la formule [I] est la 5-[3-{4-(2,2-diphénylacétyl)pipérazine-1-yl}-2-hydroxypropoxy]quinoléine.

25. Utilisation selon la revendication 17, dans laquelle le composé de formule [X] est la 5-[3-{4-(2,2-diphénylacétyl)-pipérazine-1-yl}-2-hydroxypropoxy]quinoléine.